

PART I
MECHANISM OF THE REARRANGEMENT OF FENCHONE

PART II
MECHANISM OF THE DIELS-ALDER REACTION

Thesis by
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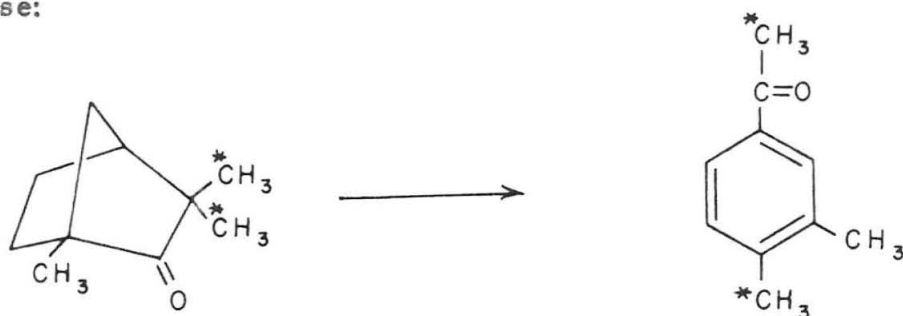
Working with Professor John D. Roberts is a unique and valuable privilege. It is a pleasure to acknowledge his interest, advice and constantly constructive criticism.

I am indebted to the California Institute of Technology for fellowships and tuition scholarships, to the National Science Foundation for a summer fellowship and to the United States Rubber Company Foundation for a terminal year fellowship.

ABSTRACT

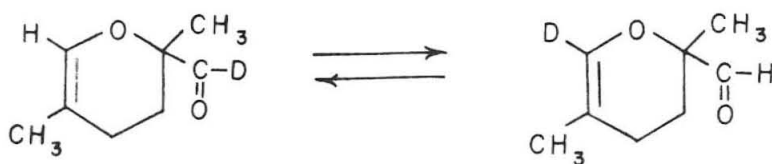
PART I

The rearrangement of fenchone (1,3,3-trimethylbicyclo[2.2.1]heptan-2-one) to 3,4-dimethylacetophenone has been carried out using a sample labeled with carbon-14 in the methyl groups of the 3-position. In concentrated sulfuric acid at 90°, 96% of the reaction takes the following course:



PART II

Optically active methacrolein dimer, labeled with deuterium at the aldehyde hydrogen, rearranges thermally with complete retention of optical activity to the isomer in which the deuterium is shifted to the vinyl position on the ring. The rearrangement is accompanied by



substantial competitive formation of methacrolein by a Diels-Alder dissociation, lending support to the presumption that this and analogous isomerizations represent partial reverse Diels-Alder reactions. The results rule out the intervention of a linear intermediate in the Diels-Alder reaction of methacrolein, and make it unlikely that similar intermediates are involved in other Diels-Alder reactions.

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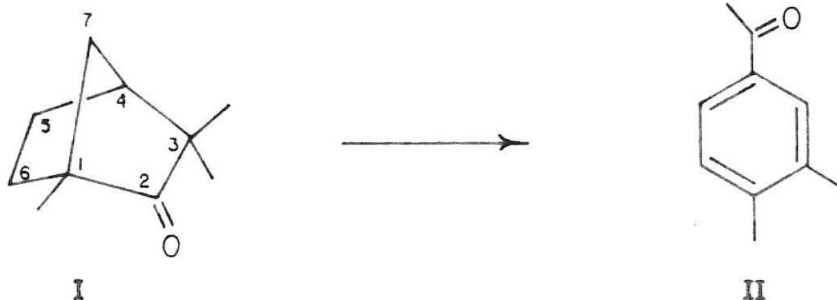
PART I

MECHANISM OF THE REARRANGEMENT OF FENCHONE

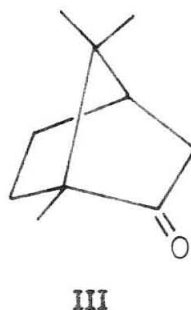
PART I

Introduction

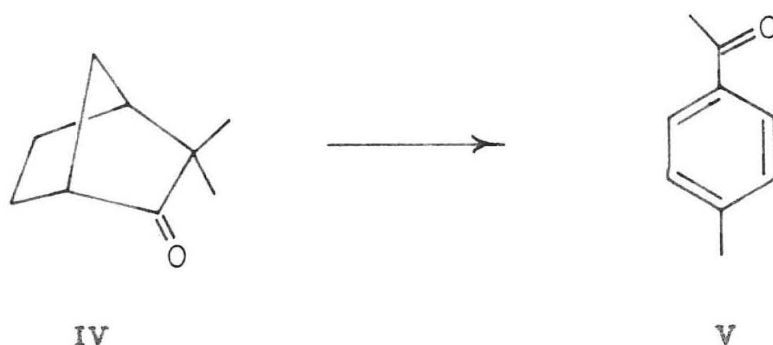
The oxidative rearrangement of fenchone (1, 3, 3-trimethyl-bicyclo[2.2.1]heptan-2-one, I) in concentrated sulfuric acid at 80-100° affords 3,4-dimethylacetophenone (II) in about 45% yield (1, 2). Under



similar conditions, camphor (III) furnishes a small amount of 3,4-



dimethylacetophenone (3,4), and camphenilone (IV) is converted to p-methylacetophenone (V) in 15% yield (5).



At first sight, the overall conversions appear to involve drastic and unusual molecular displacements, but on closer inspection they can be rationalized, as Noyce has proposed (5), by a series of more or less conventional transformations. These are illustrated in Figure 1 for the rearrangement of fenchone; wavy lines in the formulas designate bonds whose configurations are unspecified, and starred atoms trace the courses of the indicated methyl groups.

Step 1 requires no comment other than the observation that simple ketones have been found to behave as fully ionized bases in sulfuric acid (6). The 1,2-shift of the methyl group represented by Step 2 is an example of a well known process in the reactions of carbonium ions (7), and is known as a Nametkin rearrangement when it occurs in bicyclic systems (8,9)*. Step 3, the overall 1,2-shift of a hydroxyl group, has few precedents, but it undoubtedly occurs in the isotope-position rearrangement of ^{14}C -labeled benzopinacolone (VI) indicated below, under conditions similar to those used in the rearrangement of fenchone (10). However, an analogous rearrangement was not

*Reference 8 is a recent comprehensive review, mechanistically oriented, of the carbonium-ion rearrangements of bridged bicyclic systems.

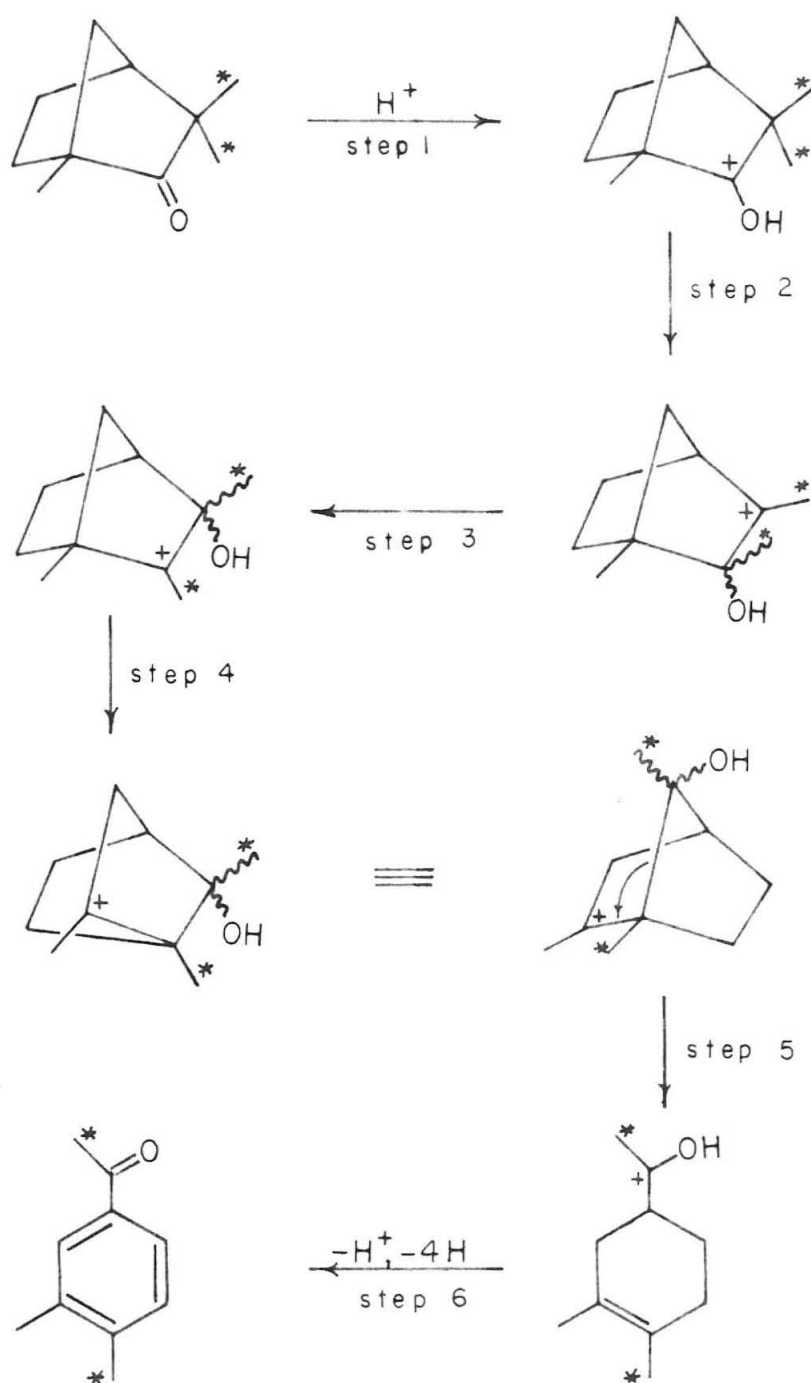
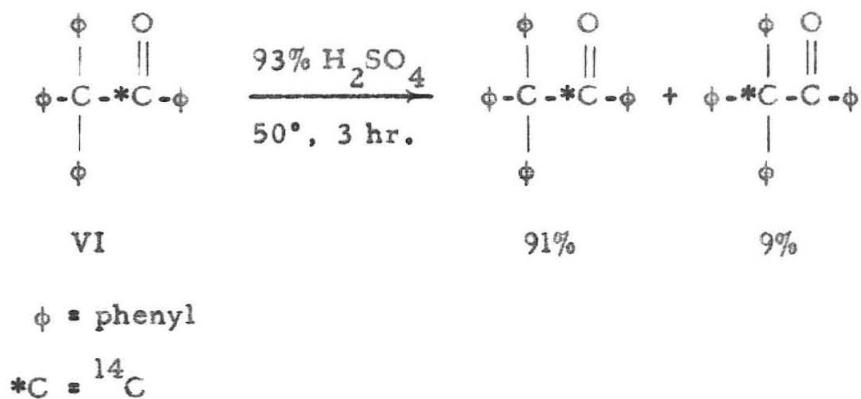
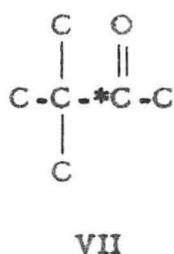


FIG. 1

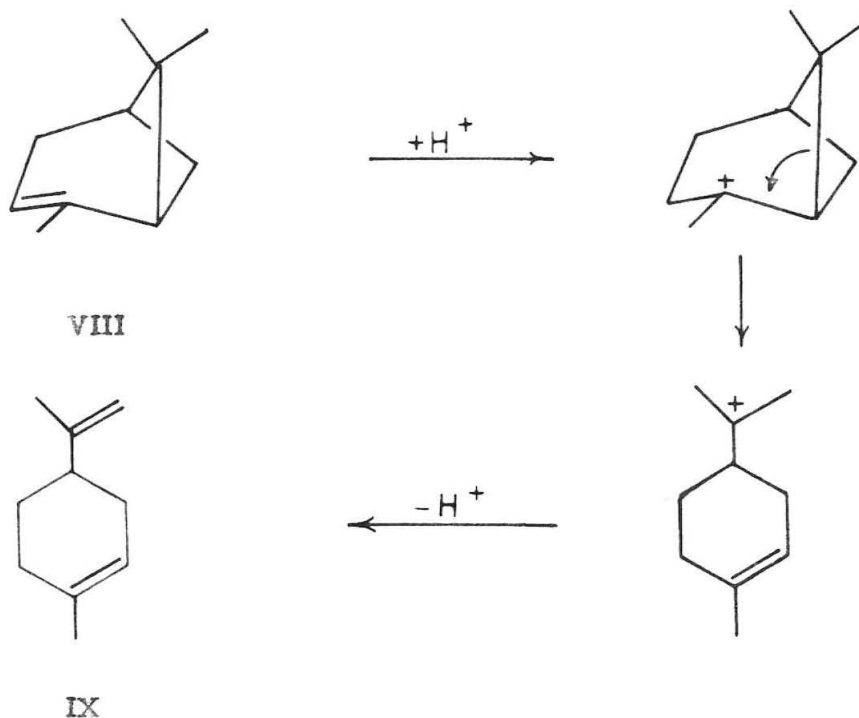


observed when labeled pinacolone (VII) was heated with concentrated

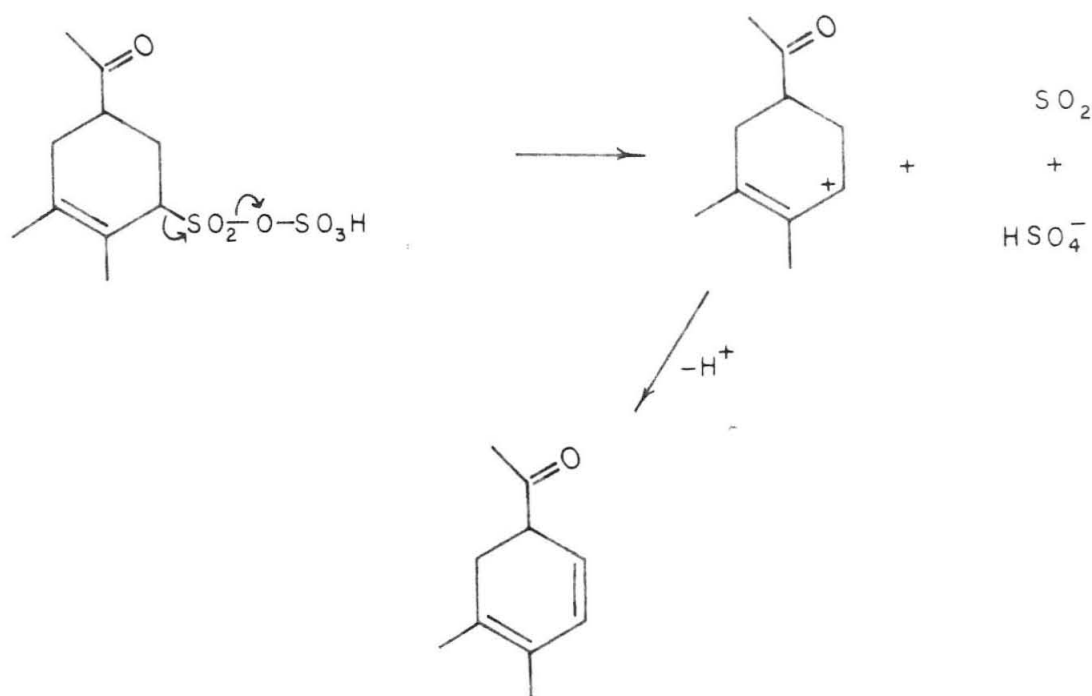


sulfuric acid for 18 days at 40° (11).

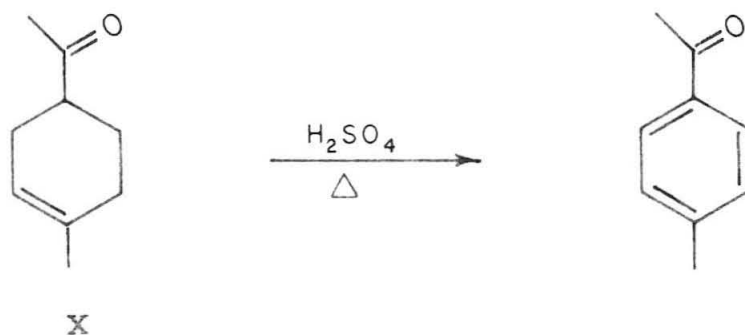
Step 4 is another example of a 1,2-alkyl shift, leading here to a rearrangement of the carbon skeleton commonly known as a Wagner-Meerwein rearrangement (8) (all 1,2-alkyl shifts are sometimes classified as Wagner-Meerwein rearrangements (12)). Step 5 is typical of fragmentations frequently encountered in the carbonium-ion reactions of substituted bicyclic compounds, another example of which is the conversion of α -pinene (VIII) to limonene (IX), among other products (13).



The final dehydrogenation in Step 6 is thought to take place by an aromatization mechanism proposed by Doering and Beringer (14) for similar reactions, according to which a pyrosulfate intermediate loses the elements of sulfur dioxide and sulfuric acid. In the rearrangement of fenchone, this mechanism could operate as follows:

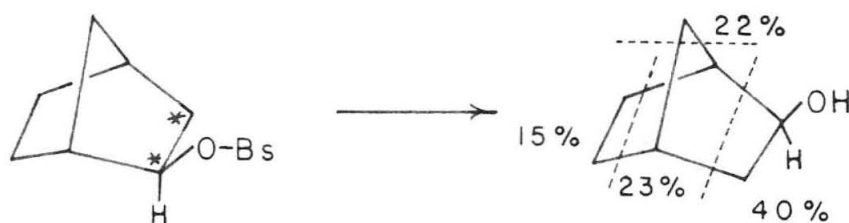


Dehydrogenation would be completed in an analogous manner. Whatever may be the precise mechanism of Step 6, the reality of an intermediate such as that leading to it is made plausible by the observation that 1-methyl-4-acetylcyclohex-1-ene (X) is converted to p-methylacetophenone by concentrated sulfuric acid (15).



Noyce has also proposed (5) that the rearrangement of camphor to 3,4-dimethylacetophenone takes place by the initial formation of fenchone which then yields product as outlined in Figure 1. A mechanism for the conversion of camphor to fenchone was not suggested, but a possible route is illustrated in Figure 2. A four-membered-ring intermediate such as XI has been proposed by Noyce to account for the formation of α -terpineol (XIII) in the nitrous-acid deamination of endo-fenchylamine (XII) (16) (Figure 3).

Although the sequence of steps shown in Figure 1 plausibly accounts for the products observed in the rearrangement of fenchone, the available evidence by no means compels acceptance of this mechanism, particularly in view of the profound skeletal rearrangements which are known to accompany the carbonium-ion reactions of even the simplest bicyclic systems. For example, Roberts, Lee and Saunders (17) have observed the following ^{14}C distribution in the alcohol obtained by lithium-aluminum-hydride reduction of the acetate produced in the acetolysis of exo-norbornyl - 2,3- ^{14}C p-bromobenzenesulfonate (XIV):



XIV

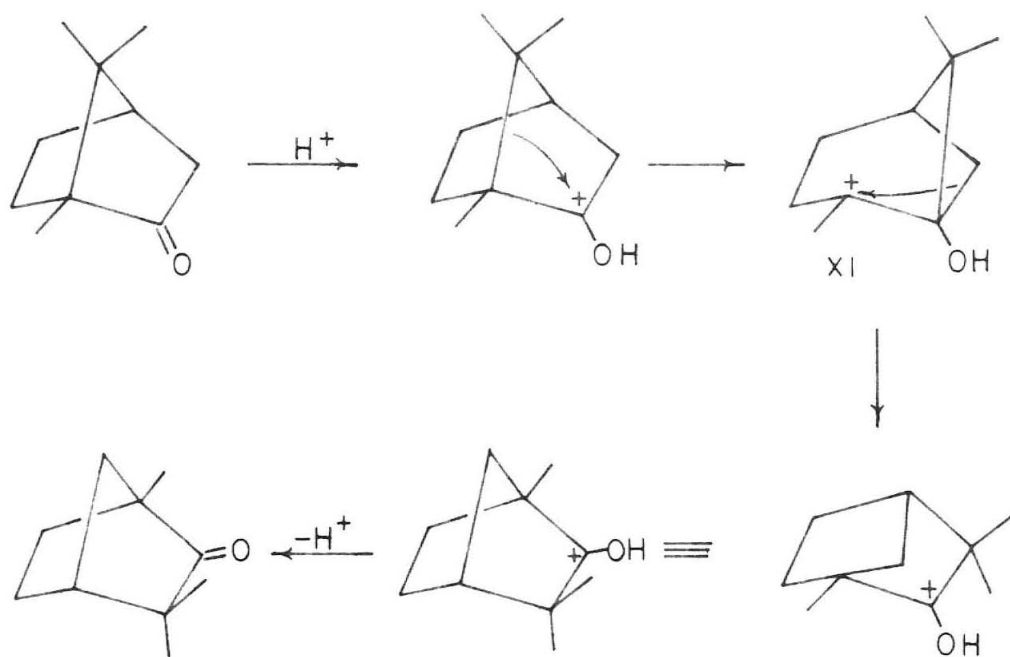


FIG. 2

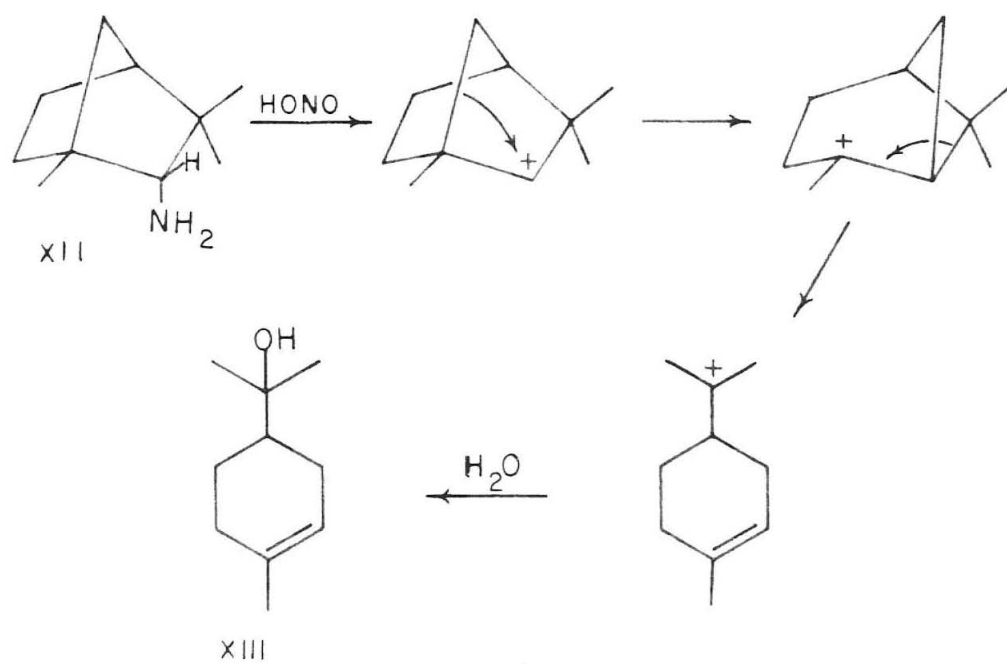
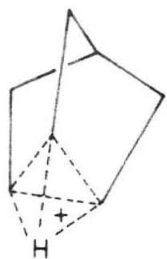
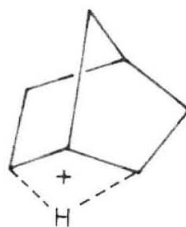


FIG. 3

The scrambling was accounted for by a combination of Wagner-Meerwein rearrangements such as Step 4 in Figure 1 and a series of overall 1,3-hydride shifts which were represented as taking place through the possible intermediacy of the ion XV or its equivalent in terms of an equilibration of ions involving intermediates such as XVI. Similar 1,3-

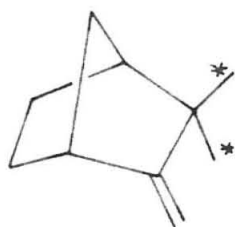


XV



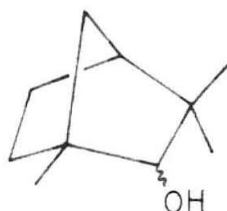
XVI

hydride shifts were postulated to compete under certain conditions with 1,2-migrations of methyl groups in the racemization of optically active ^{14}C -labeled camphene (XVII) (18), and were invoked to account for certain



XVII

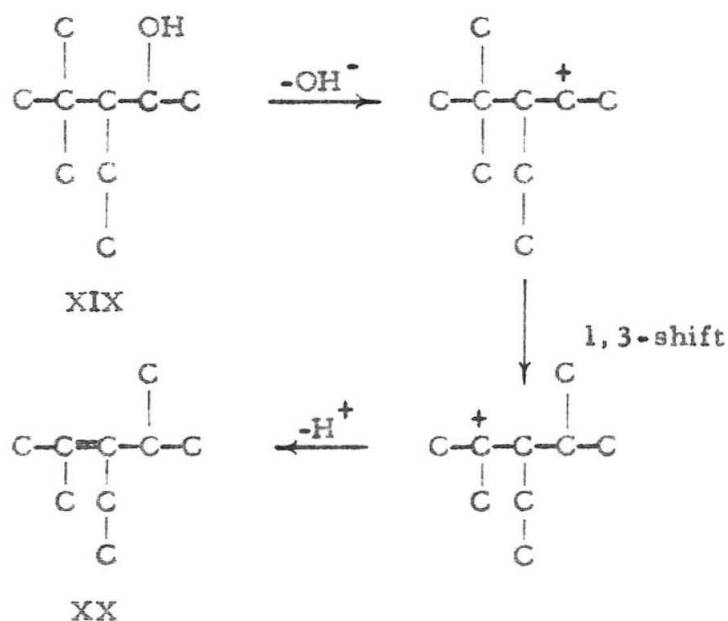
of the products observed in the dehydration of fenchyl alcohol (XVIII)(19).



XVIII

Their occurrence is fully confirmed by these and numerous other examples (20).

In addition to the potential intervention of 1,3-hydride shifts in the rearrangement of fenchone, there exists the possibility that 1,3-alkyl shifts may be involved. This type of shift, rarely observed, has been postulated to account for the formation of 2,4-dimethyl-3-ethyl-2-pentene (XX) along with unrearranged olefin in the dehydration of 4,4-dimethyl-3-ethyl-2-pentanol (XIX) (21).



In consideration of the conceivable complications discussed above, additional evidence pertinent to the mechanism of the rearrangement of fenchone was thought desirable and was obtained by rearranging a sample labeled with ^{14}C in the methyl groups of the 3-position, and determining the distribution of the label in the methyl groups of the resulting 3,4-dimethylacetophenone. According to the mechanism postulated by Noyce, the ^{14}C label (the starred atoms in Figure 1) would be equally distributed between the methyl group adjacent to the carbonyl and the one in the para position of the ring. The results of the labeling experiment have essentially verified this prediction.

In the course of this study, the complete product mixtures obtained in the rearrangement of fenchone and of camphor were examined.

Synthetic and Degradative Methods

Radioactive fenchone was prepared as outlined in Figure 4 by a procedure based on that of Beckmann and Schaber (22). The final product after dilution with inactive fenchone had an activity of $12.3 \pm 0.05 \mu\text{c}/\text{mmole}$ (as the oxime) and was rearranged by heating at 90° for 30 min. with ten times its weight of concentrated sulfuric acid. The reaction mixture was diluted with water and extracted with pentane to isolate the crude product, which was found by vapor phase

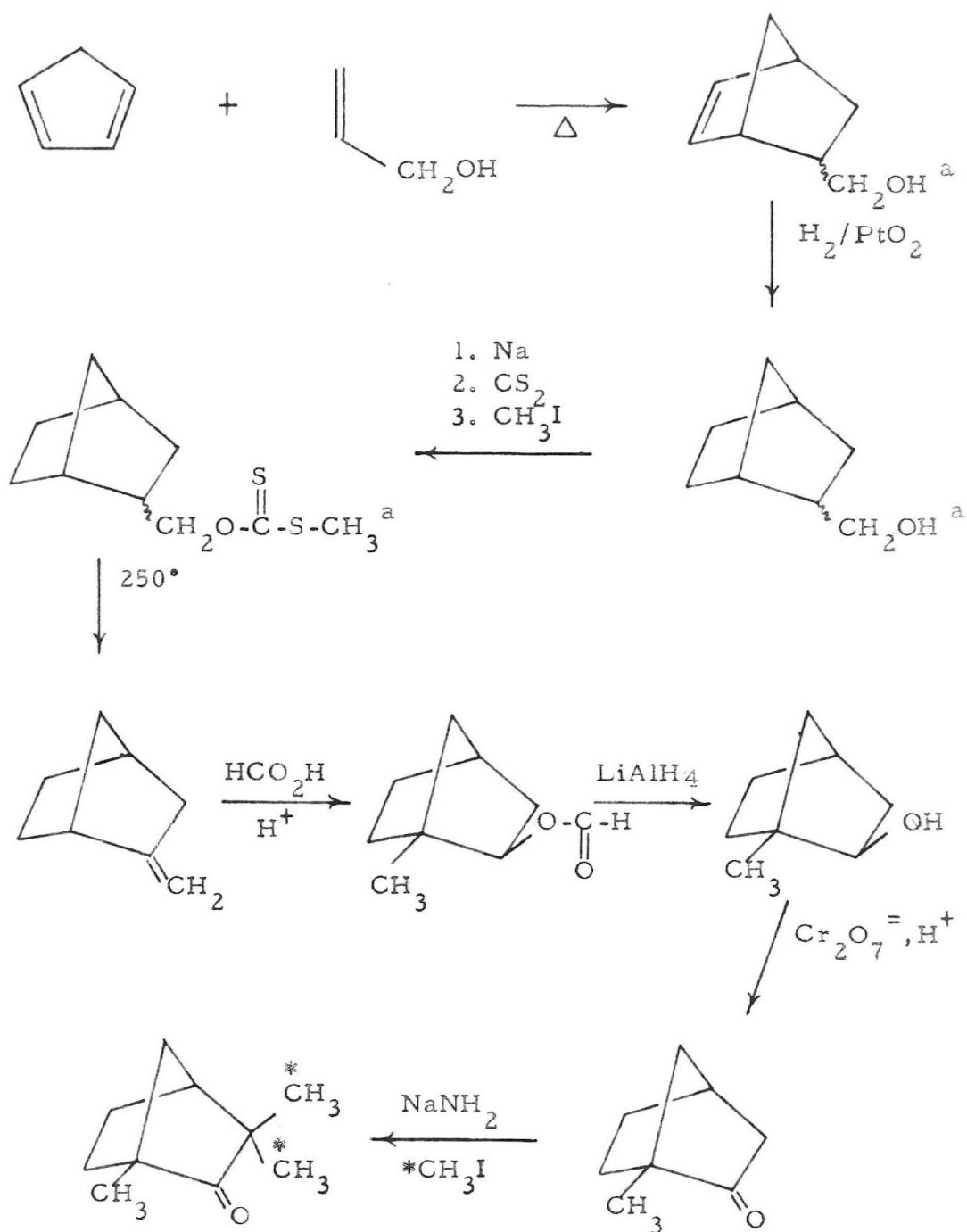


Fig. 4 - Synthesis of radioactive fenchone. ^aA mixture of the exo and endo products.

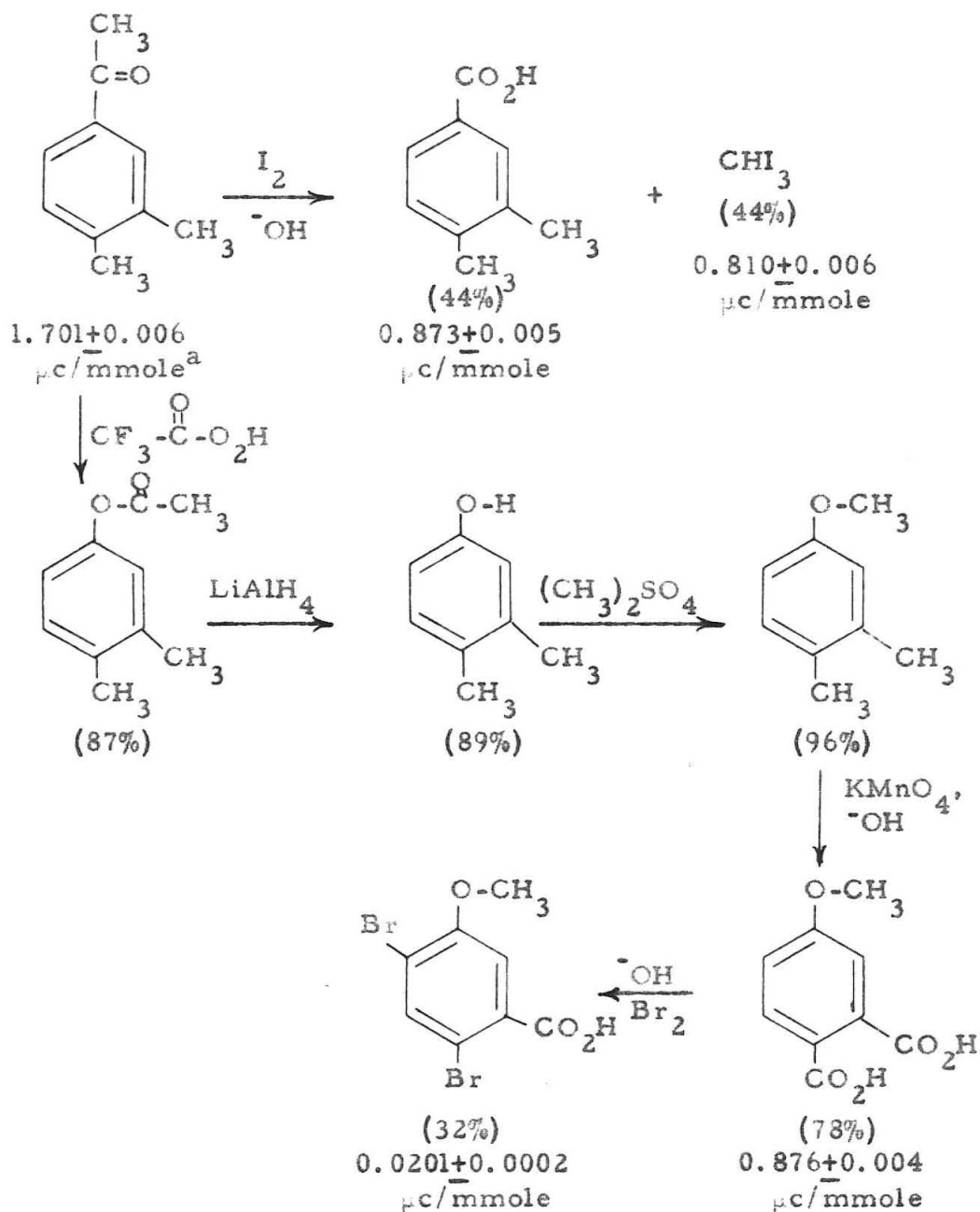


Fig. 5.— Degradation of radioactive 3,4-dimethylacetophenone.

Activities are in microcuries per millimole ($\mu\text{c/mmole}$) and were determined by the vibrating-reed electrometer method as described by O. K. Neville, *J. Am. Chem. Soc.*, **70**, 3499-3502 (1948). Errors are expressed as average deviations in the case of duplicate determinations or as standard deviations when three or more measurements were made (see Experimental). ^a Measured as the 2,4-dinitrophenylhydrazone; all other compounds whose activities are indicated were assayed directly.

chromatography (v. p. c.) (Fig. 7-A) to contain about 70% of 3, 4-dimethylacetophenone in addition to several other components whose identity is discussed in a later section. Inactive 3, 4-dimethylacetophenone was added to the mixture to facilitate isolation of the radioactive sample. The yield of radioactivity in the rearrangement was 44%.

The degradation of the radioactive 3, 4-dimethylacetophenone and the activities of the degradation products are summarized in Figure 5; reaction yields are given in parentheses. The radioactive samples were not diluted with inactive material at any stage of the degradation.

Results and Discussion

The distribution of radioactivity in the ^{14}C -3, 4-dimethylacetophenone is summarized in Figure 6. The sum of the activities

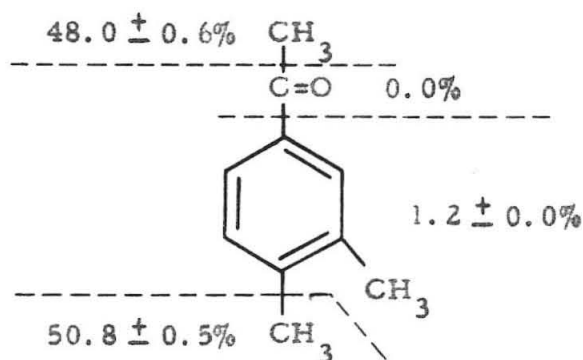


Figure 6

of iodoform and of 4-methoxy-1,2-benzenedicarboxylic acid was taken as 100%, and the radioactivity in the 4-methyl group was taken as the difference between the value for 4-methoxy-1,2-benzenedicarboxylic acid and that for 2,4-dibromo-5-methoxybenzoic acid. It is assumed that the activity of the latter represents the activity of the 3-methyl group. If the radioactivity in the 4-methyl group is actually significantly greater than 50%, it may represent the operation of a small ^{14}C -isotope effect in the decarboxylation reaction (23). The agreement between the activities of 3,4-dimethylbenzoic acid and 4-methoxy-1,2-benzenedicarboxylic acid indicates that isotope effects were not important in the rest of the degradation sequence.

The results of the tracer experiment show that about 96% of the rearrangement can be accounted for by the mechanism discussed in the Introduction; this appears to be the most reasonable and straightforward way of representing the transformation. The remaining 4% involves either a different pathway (one possibility is presented on page 24) or a prior equilibration of the 1-methyl group in fenchone with one, but not both, of the methyl groups in the 3-position.

The major by-product of the rearrangement of fenchone was the isomer, camphor, identified by its infrared spectrum and retention time in vapor phase chromatography (Figure 7-A). When camphor was treated with sulfuric acid under conditions identical to those of the fenchone rearrangement, fenchone was one of the products (Figure 7-B),

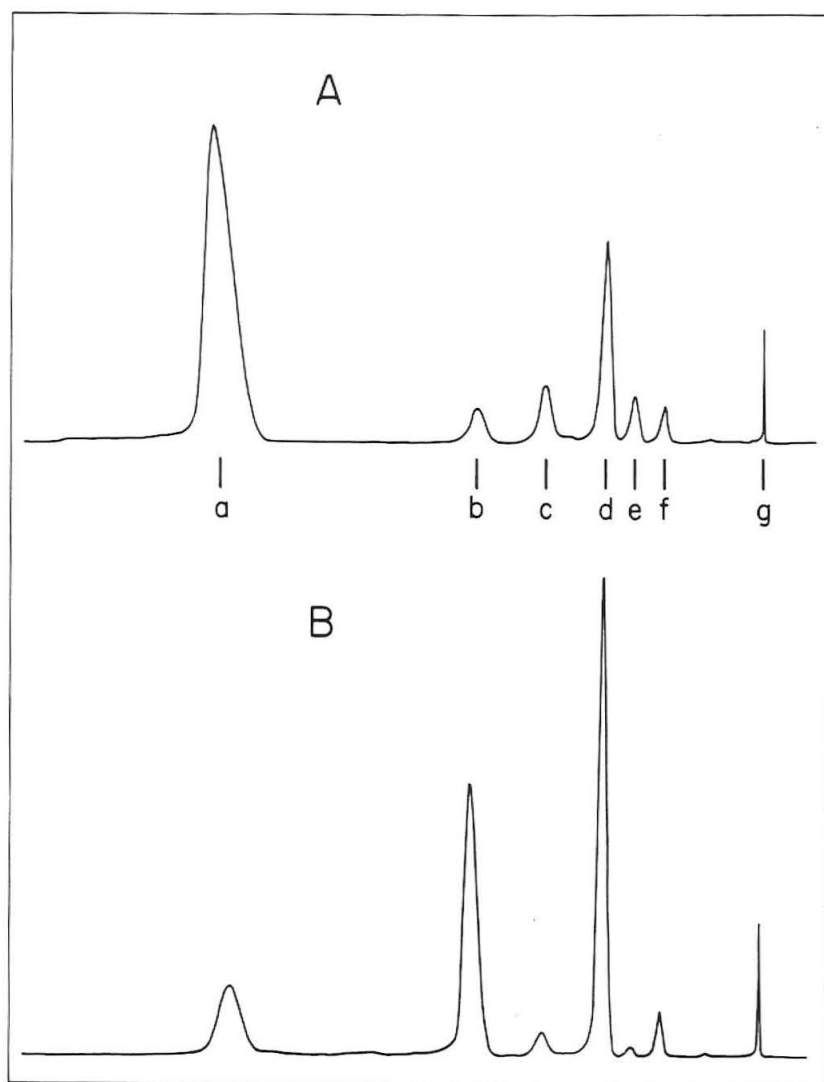
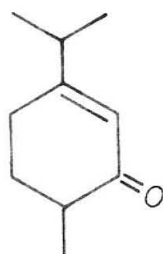
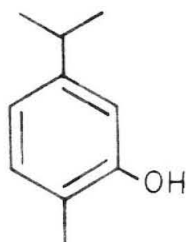


Fig. 7. — Vapor-phase chromatograms of rearrangement product mixtures analyzed at 190° using polyethylene glycol (Carbowax 1500) on a diatomaceous earth support. The indicated peaks represent the following compounds: (a), 3,4-dimethylacetophenone; (b), carvenone; (c), unidentified; (d), camphor; (e), unidentified; (f), fenchone; (g), solvent. The distance between a and g on the time scale is 17 min. (A) - Rearrangement of fenchone at 90° for 30 min. (B) - Rearrangement of camphor at 90° for 1 hr.; the same mixture, except for relative proportions, was obtained after 30 min. at 90° .

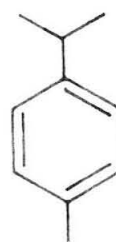
lending credence to the suggestion of Noyce that fenchone is an intermediate in the rearrangement of camphor to 3,4-dimethylacetophenone. The same mixture was obtained in both rearrangements, although the relative proportions of the individual components were different. The major product of the camphor rearrangement, in addition to 3,4-dimethylacetophenone, is known to be carvenone (XXI) (4); the designated peak was assigned on this basis. Carvacrol (XXII) and *p*-cymene (XXIII) have been formed from camphor under either dehydrating or acidic



XXI



XXII



XXIII

conditions (24), but authentic samples of these compounds could not be correlated by their v.p.c. retention times with the other by-products in the rearrangements of fenchone and camphor.

Subsequent to Noyce's formulation of the mechanism for the rearrangement of fenchone, there have been made important discoveries concerning the nature of the intermediates involved in the carbonium ion reactions of bicyclic compounds (8); of particular interest is the evidence which has led to the acceptance of bridged ions as

accurate representations of these intermediates (17, 25)*. Although the results of the ^{14}C -tracer experiment provide no new information in this regard, the mechanism for fenchone rearrangement may be reformulated in the more sophisticated manner shown in Figure 8, starting from a first-formed bridged ion (XXIV). Because of the partial bond between C-6 and C-2, migration to ion XXV probably involves the exo-methyl group. Formation of ion XXVI then requires the overall endo migration of the hydroxyl group, but this transformation is not likely to be severely impeded by the partial bond between C-5 and C-3 since this bond is weak (because it concentrates positive charge at a secondary center) with respect to the bond between C-5 and C-4 (which concentrates positive charge at a tertiary center). Fragmentation of ion XXVI as shown leads to XXVII which could dehydrogenate as suggested previously.

The interconversions of fenchone and camphor may be reformulated in a similar fashion (Figure 9), starting with the ion XXVIII which should be formed less readily than XXIV since the strained four-membered ring structure implied by the partial bond between C-7 and C-2 is relatively less stable than the structures implied by the other partial bonds in XXIV and XXVIII.

*For a detailed description of the bridged ion, see reference 8. Streitwieser (26) gives a pictorial orbital representation.

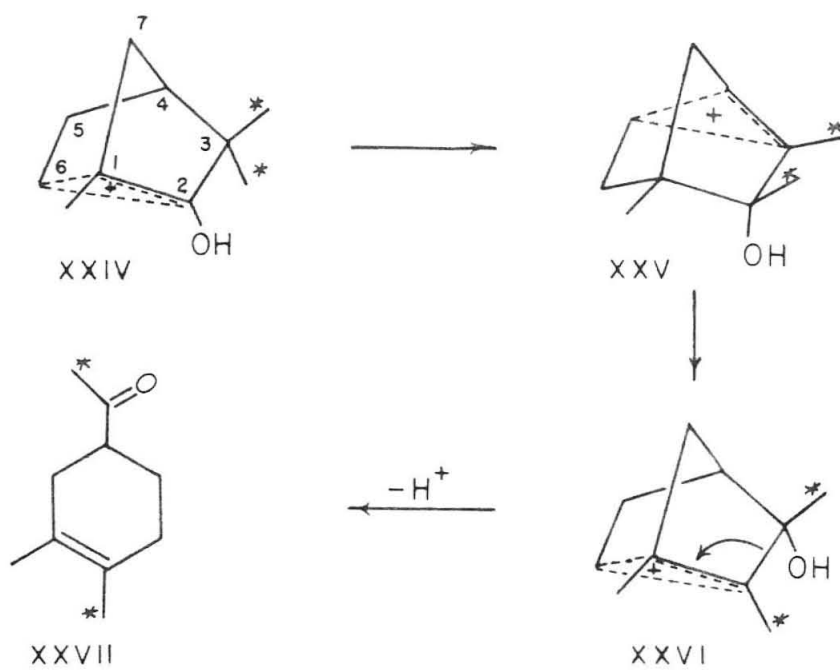


FIG. 8

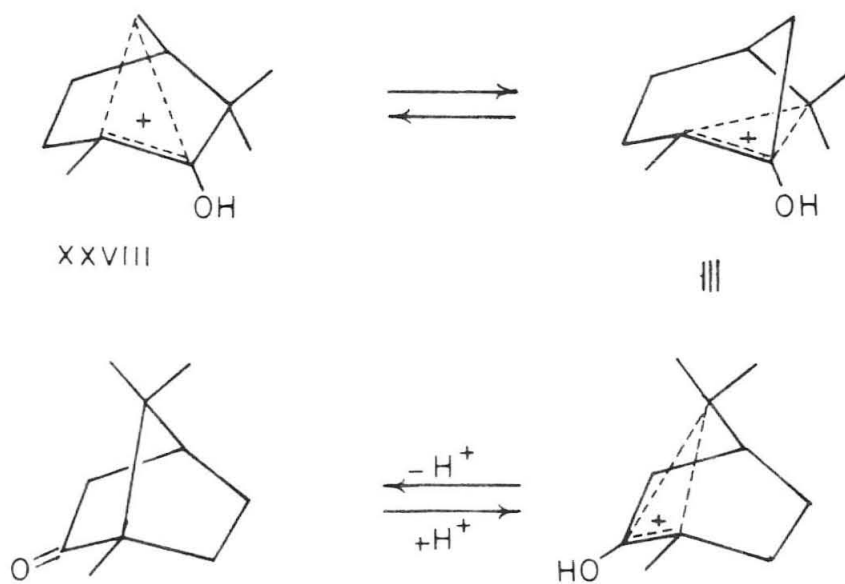
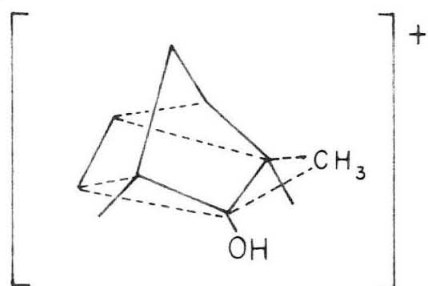
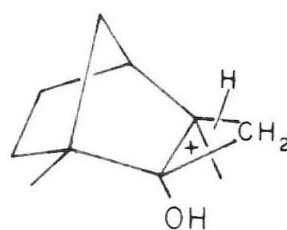


FIG. 9

On the basis of evidence obtained in other systems, it is possible to speculate on the existence of intermediates such as XXIX or XXX,

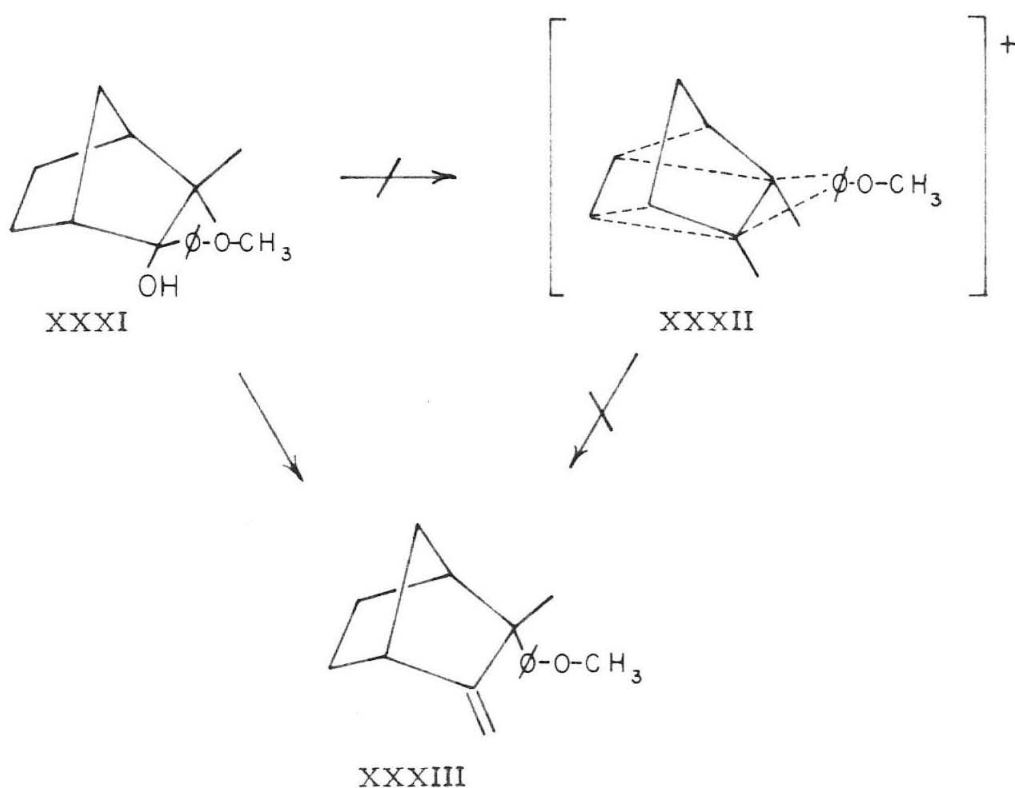


XXIX

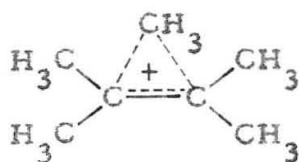


XXX

which could conceivably take part in the 1,2-alkyl shift which converts XXIV to XXV. The available information requires neither of these formulations. In the reaction of 2-*p*-anisylcamphenilol (XXXI) to yield 2-*p*-anisylapocamphene (XXXIII), the symmetrical intermediate XXXII

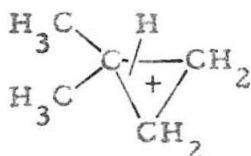


was not involved since the product was optically active (27). (The intermediate XXXII is not strictly analogous to XXIX, however, since formation of XXXII requires an initial relatively unfavorable migration of an endo-methyl group.) The symmetrical bridged intermediate XXXIV was found not to be important in the carbonium ion reactions of penta-methylethyl derivatives (28).



XXXIV

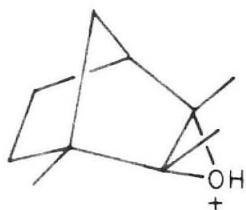
It has been concluded (29, 30) that protonated cyclopropanes such as XXXV, analogous to XXX, are not intermediates in the neopentyl



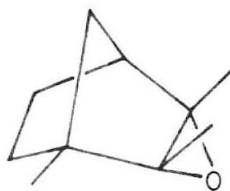
XXXV

carbonium ion system.

For the conversion of XXV to XXVI, possible intermediates are the protonated and unprotonated oxides, XXXVI and XXXVII. There is at present no proof that either of these is an intermediate in the fenchone rearrangement, or that similar species are intermediates in the isotope-position rearrangement of ^{14}C -benzopinacolone (VI) (10)

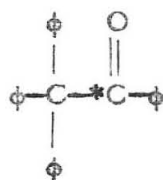


XXXVI



XXXVII

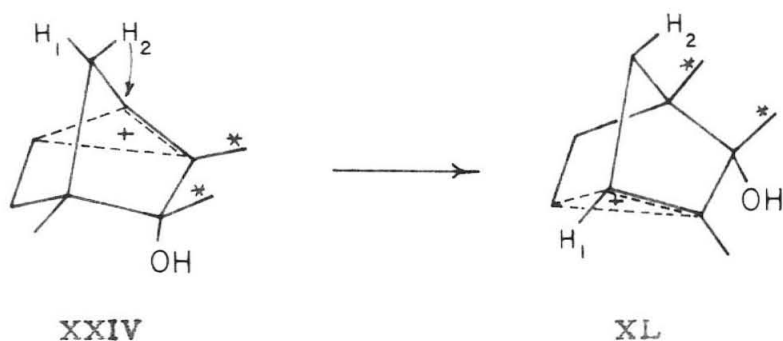
or other acid-catalyzed rearrangements of ketones (31).



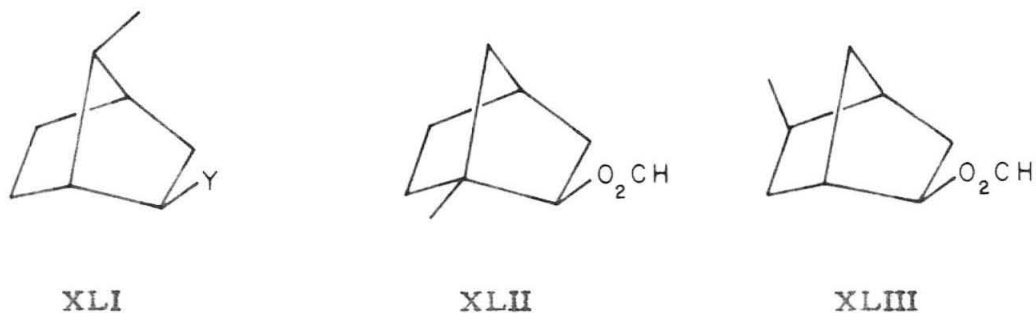
VI

The approximately 4% of reaction in the rearrangement of fenchone which leads to radioactivity which is assumed to be in the meta-methyl group at the expense of the methyl group adjacent to the carbonyl may be rationalized by the sequence of steps shown in Figure 10. Other schemes could undoubtedly be devised, but the advantage of the one given is that only one additional transformation is required over those proposed as the main reaction path. For the purpose of clarity, bridged structures are not explicitly formulated, but are implied wherever applicable.

Species XXXVIII is formed by a relatively unfavorable Wagner-Meerwein rearrangement leading from a tertiary to a secondary carbonium ion. A 1,2-hydride shift converts XXXVIII to XXXIX. In terms of bridged structures, the critical transformation is the conversion of XXIV, involved in the main reaction path, to its mirror image (except for ^{14}C), XL.



Similar 1,2-hydride migrations, although frequently encountered in other carbonium-ion systems (32), are rarely observed with bicycloheptane derivatives. One rearrangement which does appear to involve this type of shift occurs in the formolysis of syn-7-methyl-2-exo-norbornyl acid phthalate (XLI, Y = acid phthalate) (33). The products are 1-methyl-2-exo-norbornyl formate (XLII) and 5-exo-methyl-2-exo-norbornyl formate (XLIII); the latter may be derived by the conventional



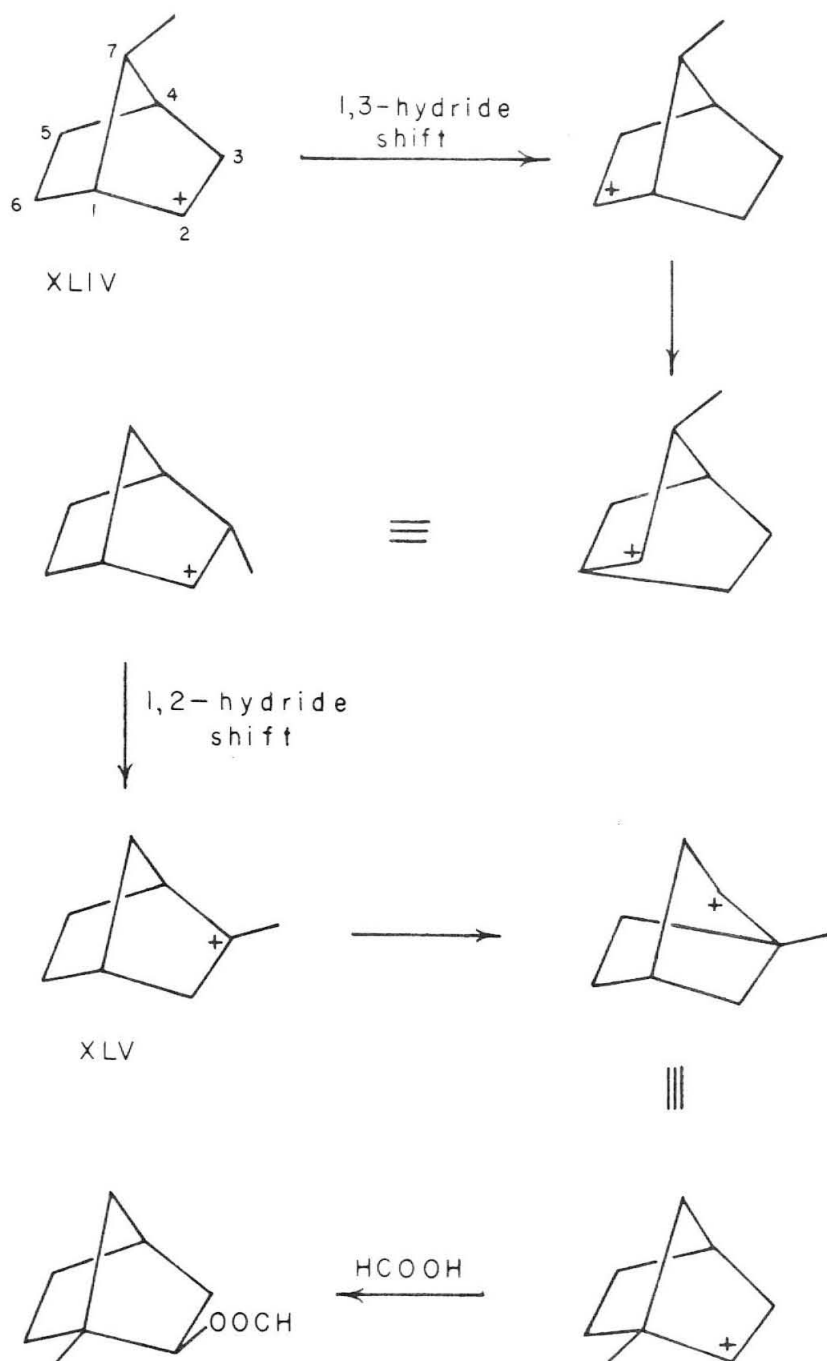
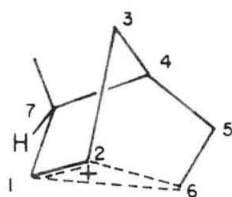


FIG. II

combination of Wagner-Meerwein rearrangement and 1,3-hydride shift. A plausible route for the former is given in Figure 11 (starting from the first-formed carbonium ion (XLIV) represented for clarity as the unbridged structure). A shorter route for obtaining the intermediate XLV (actually its mirror image) from XLIV, shown below as the



XLIV

bridged structure, would be the direct 1,2-migration of the endo hydrogen at C-7, but this path is thought to be relatively less likely because of interference to migration by the partial bond between C-6 and C-1 (8).

Apparently the familiar 1,3-hydride shifts are not involved in the rearrangement of fenchone in either the main reaction path or the accompanying reaction leading to a different isotope distribution.

Experimental

Preparation of ^{14}C -Labeled Fenchone*

2-Hydroxymethylbicyclo[2.2.1]hept-5-ene.— Dicyclopentadiene (119 g., 0.902 mole) and allyl alcohol (116 g., 2.00 mole) were sealed into a 500-ml. stainless-steel autoclave and were heated under autogenous pressure for 15 hr. at 165-180°. The reaction was repeated using the same quantities of materials, with heating at 175-180° for 11 hr. The combined crude products were dried over anhydrous calcium chloride and distilled through a 10-in. Vigreux column equipped with a variable take-off head; 217 g. (49% yield and conversion) of product was collected at 89-95° (13 mm.), with practically all boiling at 93-94° (13 mm.), lit. (34) b.p. 92-95° (13 mm.). Analysis by v.p.c. (Column A, 174°) indicated that the product consisted of greater than 90% of a mixture of two poorly resolved components, probably the exo and endo isomers of the alcohol.

2-Hydroxymethylbicyclo[2.2.1]heptane.— A total of 213 g. (1.72 mole) of 2-hydroxymethylbicyclo[2.2.1]hept-5-ene as a 10% solution in dry ethyl acetate was hydrogenated at room temperature in a Parr shaking apparatus using platinum oxide catalyst. The hydrogen-

*Based on the procedure of Beckmann and Schaber (22).

ation was carried out in several batches, each time (except the last) using 25 g. of the unsaturated alcohol and 0.25 g. of platinum oxide. The catalyst was recovered and used in subsequent runs; only two separate portions were used. Hydrogenation was complete in about 5 min. with fresh catalyst (starting at 52 psig.), and about 10 min. with used catalyst.

The crude product, after removal of the ethyl acetate, was distilled through a 10-in. Vigreux column equipped with a variable take-off head. The yield of material boiling at 95-97.5° (13 mm.) was 206 g. (95% ; lit. (34) b.p. 95-96° (13 mm.)). Analysis by v.p.c. (Column A, 165°) showed one main peak whose area was about 95% of the total peak areas.

2-Methylenebicyclo[2.2.1]heptane (Norcamphene).— The saturated alcohol from the above preparation was converted to norcamphene in three separate reactions; the most satisfactory procedure is reported here.

Ten grams (0.43 mole) of sodium was added to 50 g. (0.40 mole) of the saturated alcohol dissolved in 50 ml. of dry toluene; a slow evolution of hydrogen began immediately. The mixture was slowly heated to reflux and maintained there for 21 hr. A solid alcoholate began to precipitate after about 2 hr. The mixture was cooled to room temperature, the excess sodium removed mechanically, and 150 ml. of anhydrous ether added followed by 40 g. (0.53 mole) of carbon disulfide.

The mixture was maintained at reflux for 4 hr., with occasional interruptions to stir the viscous mass and break up the lumps of alcoholate. For the last hour, the suspension was stirred magnetically. It was then cooled in ice and 60 g. (0.42 mole) of cold methyl iodide was added in small increments. The mixture was stirred at reflux for 4 hr., then overnight at room temperature.

The sodium iodide was allowed to settle, and as much of the supernatant liquid as possible decanted and gravity filtered. The solids in the remaining sludge were dissolved in the minimum amount of water and the resulting mixture extracted twice with ether. The extracts were combined with the main ether solution which was then dried over anhydrous sodium sulfate and distilled without fractionation to remove ether. Most of the toluene was removed under the reduced pressure of a water aspirator, and the crude xanthate distilled through a short Vigreux column to yield 22 g. of forerun boiling at 95-167° (14.5 mm.) and 62 g. (72% yield) of the xanthate ester boiling at 167-169° (14.5 mm.), lit. (35) b.p. 182° (15 mm.).

Pyrolysis of the xanthate was carried out in 10 ml. of magnetically stirred silicone oil (General Electric SF-81(50)) in a 100-ml. flask equipped with an addition funnel and a small Claisen head and condenser with an ice-cooled receiver connected to a Dry-Ice trap. The silicone oil was heated to 250° and the xanthate added dropwise. The decomposition products distilled out of the mixture, and heating at 250° was

continued after the completion of addition of the xanthate until no more liquid distilled. The last of the product was brought over under reduced pressure. The contents of the Dry Ice trap were evaporated into a second trap and the liquid remaining at room temperature was combined with the main sample of crude product; the total was taken up in 25 ml. of ether and washed with two 25-ml. portions of 10% aqueous sodium carbonate. The aqueous washings were extracted once with 10 ml. of ether, and the combined ether solutions dried over anhydrous sodium sulfate and distilled out of freshly cut sodium through a short Vigreux column. The material boiling at 120-122° was redistilled from sodium and yielded 21.7 g. of norcamphene boiling at 121-122° (749 mm.), n_D^{25} 1.4715 (lit. (22) b.p. 123°, n_D^{25} 1.4719). Analysis by v.p.c. (Column A, 95°) indicated a product of greater than 97% purity; the yield was 50% based on the starting alcohol and 70% based on the xanthate used in the pyrolysis.

1-Methyl-exo-bicyclo[2.2.1]hept-2-yl Formate (1-Methyl-exo-norbornyl Formate).— In the procedure of Beckmann and Schaber (22), norcamphene was converted to 1-methyl-exo-norborneol by the acid-catalyzed addition of acetic acid to norcamphene and subsequent saponification of the acetate with methanolic potassium hydroxide; the resulting alcohol was reported to be homogeneous 1-methyl-exo-norborneol. In the present work, it was found that the lithium-aluminum-hydride reduction of the acetate yielded a mixture which was shown by v.p.c.

(Column K, 144°) to contain about 65% of 1-methyl-exo-norborneol and 35% of 2-methyl-2-hydroxynorbornane. The structure of the latter was assigned on the basis of its acid-catalyzed equilibration with 1-methyl-exo-norborneol. Variations in the experimental conditions for the preparation of the acetate resulted in only minor changes in the proportion of the two products, but about 95% of 1-methyl-exo-norborneol could be obtained by preparation and reduction of the formate ester. A representative procedure is given here.

Norcamphene (10.5 g., 0.0972 mole) was stirred and heated at 60-65° for 11 hr. with 30 g. of 90% formic acid containing 10 drops of 50% fluoboric acid. The solution was diluted with 200 ml. of water and extracted with 60 ml. of ether in three portions. The combined ether extracts were dried over anhydrous sodium sulfate and used directly in the following reaction.

1-Methyl-exo-norborneol.— The ether solution of the formate was added dropwise to 4.0 g. (0.11 mole) of lithium aluminum hydride suspended with stirring in 30 ml. of anhydrous ether. Stirring was continued for 7 hr. after the completion of addition (several hours required for complete reaction). The excess hydride was decomposed with water and the mixture was acidified with 10% hydrochloric acid. The ether layer was decanted and the aqueous layer extracted twice with ether, then continuously with pentane. The combined ether solutions were dried

over anhydrous sodium sulfate and distilled to remove the solvent. The pentane solution was dried and distilled to yield a small amount of product which was combined with the main sample, which was then subjected to high vacuum (less than 1 mm.) to remove the last of the solvents. The remaining material, shown by v.p.c. (Column K, 144°) to consist of a quite pure mixture of the two alcohols containing about 95% of 1-methyl-exo-norborneol, weighed 11.5 g. (94% yield) and was used without further purification.

1-Methylbicyclo[2.2.1]heptan-2-one (1-Methylnorcamphor).-

The conversion of 1-methyl-exo-norborneol to the ketone was carried out in several reactions under varying conditions. The following is representative of a satisfactory procedure.

Alcohol from the above preparation (11.5 g., 0.0913 mole) was dispersed with a magnetic stirrer in 75 ml. of water containing 4 g. of sulfuric acid. To the stirred mixture was added over a period of 2.5 hr. a solution of 8.9 g. (0.030 mole) of potassium dichromate and 10 g. of sulfuric acid in 100 ml. of water; the mixture was stirred at room temperature for a total of 36 hr. The progress of the reaction was followed by allowing the phases to separate and examining the organic liquid by v.p.c. (Column K, 145°); after the first 12 hr., an additional 4.0 g. (0.014 mole) of potassium dichromate in 30 ml. of water was added, and at one point about 12 hr. before the completion

of reaction, the mixture was heated at 50° for 1 hr.

The organic layer was taken up in pentane and the aqueous layer extracted twice, then continuously extracted overnight, with pentane. The combined pentane solutions were dried over anhydrous sodium sulfate and distilled to remove solvent. The crude product was distilled through a 25-cm. Wheeler center-rod column to yield, after 0.4 g. of forerun, 3.6 g. of 1-methylnorcamphor boiling at 58-59° (11.5 mm.) and 0.7 g. of a higher-boiling fraction. The main fraction contained less than 2% of impurities by v.p.c. (Column K, 141°); the impure fractions were combined for distillation with the crude product from a subsequent run. The yield of 1-methylnorcamphor, including the estimated amounts in the impure fractions, was 40%.

In other runs, the 1-methylnorcamphor in impure fractions was isolated by preparation of the semicarbazone and regeneration of the ketone using pyruvic acid. A sample of 1-methylnorcamphor semicarbazone recrystallized three times from 50% aqueous ethanol had m.p. 201-202° (lit. (22) m.p. 209°).

Anal. Calcd. for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19.

Found: C, 59.73; H, 8.37; N, 22.85.

^{14}C -Methyl Iodide from ^{14}C -Methanol.— In a representative reaction, 3.77 g. (0.118 mole) of methanol with an activity of about 16 μ c/mmole was dissolved in 50 ml. of 55-58% hydroiodic acid in a 100-ml. flask equipped with a 30-cm. wire-spiral-packed column with

an ice-water-cooled condenser and Dry-Ice-cooled receiver protected by a Dry Ice trap. The reaction mixture was maintained at about 65° for two hours while the product distilled as it formed. The mixture was gradually heated to 80°, and the last of the product was distilled out of solution under reduced pressure. The crude product was distilled without fractionation from phosphorous pentoxide to yield 14.9 g. (89%) of methyl iodide which was shown by v. p. c. (Column A, 70°) to be about 99% pure.

1-Methyl-3, 3-di-(¹⁴C-methyl)bicyclo[2.2.1]heptan-2-one
(Radioactive Fenchone).— To an ice-cold magnetically stirred suspension of sodamide in 50 ml. of ether, prepared by the procedure described by Vogel (36) from liquid ammonia and 3.1 g. (0.13 mole) of metallic sodium, was added 4.5 g. (0.036 mole) of 1-methylnorcamphor. The mixture was heated at reflux for 1.5 hr., cooled in an ice bath, and 7.0 g. (0.049 mole) of radioactive methyl iodide (about 16 μ c/mmole) was added all at once, causing the immediate precipitation of a white solid. The mixture was heated at reflux for 1 hr., the coolant (ice water) then drained out of the reflux condenser, and the ether and excess methyl iodide were allowed to distill over to be collected at -78°. The last of the low-boiling liquids was brought over under reduced pressure. In a pilot reaction prior to this particular run, a sample of the residue remaining after removal of ether and methyl iodide was quenched with water and the ketone mixture isolated by extraction with pentane and

removal of the solvent. Analysis by v.p.c. (Column C, 162°) showed that it contained about 40% of fenchone, 60% of fenchosantenone (1,2-dimethylbicyclo[2.2.1]heptan-2-one) and a trace of 1-methylnorcamphor.

The residue was cooled in ice, and a freshly prepared suspension of sodamide (from 3.1 g. (0.13 mole) of sodium) in 50 ml. of ether added. The mixture was refluxed for 1.5 hr., then cooled in ice; 4.4 g. (0.31 mole) of the radioactive methyl iodide was added and reflux continued for an additional 30 min. At this point was added 15 g. of a 17% (by weight) solution of radioactive methyl iodide (2.6 g., 0.018 mole) in ether; this solution was recovered from a previous preparation of radioactive fenchone and was used as such, since it was found impractical to separate the methyl iodide from the solvent ether. Reflux was continued for 1 hr., then the ether and excess methyl iodide were removed as before.

The excess sodamide was cautiously decomposed by the dropwise addition of water, and the mixture acidified with 10% sulfuric acid (until the 100-ml. reaction vessel was almost full) followed by the dropwise addition of concentrated sulfuric acid. The organic layer was examined by v.p.c. (Column A, 167°) and found to contain about 75% of fenchone, 13% of 1-methylnorcamphor and 12% of what are believed to be exo- and endo-fenchosantenone.

Inactive fenchone (4.5 g.) was added to the reaction mixture and the total continuously extracted for 28 hr. with pentane. The pentane

was removed by distillation, and the residue set aside for 45 hr. in 30 ml. of methanol containing the semicarbazide acetate prepared by triturating 4.5 g. of semicarbazide hydrochloride with 6.8 g. of anhydrous sodium acetate. (Fenchone forms the semicarbazone very slowly, whereas 1-methylnorcamphor and fenchosantenone react readily) The solution was diluted with 100 ml. of water, extracted with two 40-ml. portions of pentane and continuously extracted for 48 hr. with pentane. The pentane solution containing the principal sample of product was filtered to remove semicarbazone which had separated out within one day, dried over anhydrous sodium sulfate and distilled to remove solvent. The crude fenchone was distilled through a short Vigreux column to yield 0.20 g. of forecut, 6.75 g. boiling at 69-72° (11 mm.) and 0.15 g. which was distilled using the full pump vacuum with strong heating of the pot and column. Analysis by v.p.c. (Column A, 168°) indicated that the forerun contained about 10% of low-boiling impurities and that the other fractions contained less than 1% of impurities.

The pentane solution from the continuous extraction was separated from precipitated semicarbazones, dried and distilled; the residue, found by v.p.c. to contain a large proportion of impurities, was treated as before with semicarbazide acetate. The fenchone which was isolated and distilled (0.40 g.) contained less than 1% of impurities. The combined weights of all the fenchone fractions represent a yield of 55% for the

methylation reaction if it is assumed that the inactive fenchone added to the crude product mixture was recovered quantitatively.

The oxime of the radioactive fenchone was prepared in 86% yield by heating a sample, quantitatively diluted with inactive fenchone, with hydroxylamine hydrochloride in pyridine solution on the steam bath for 8 hr., and subliming the crude product; m.p. 159-160° (sealed capillary; lit. (22, 37) m.p. of the α -oxime, 158-160°). Radioactivity analysis (duplicate) indicated an activity for the undiluted fenchone of $12.3 \pm 0.05 \mu\text{c/mmole}$.

Rearrangement of Radioactive Fenchone

A sample of radioactive fenchone (6.52 g., 0.0429 mole) was added all at once to 35 ml. of 95.5-96.5% sulfuric acid maintained at 90° and the mixture was magnetically stirred and heated at 90° for 30 min.; during this period a gas possessing the characteristic odor of sulfur dioxide was evolved. The dark-brown reaction mixture, containing a considerable amount of charred material, was cooled to room temperature, poured over crushed ice, diluted to about 400 ml., and continuously extracted with pentane for 24 hr. A sample of the extract was withdrawn, the solvent removed, and the residue examined by v.p.c. (Column K, 192°; see Fig. 7-A). The boiler was replaced with a flask of fresh pentane, 5.0 g. of inactive 3,4-dimethylacetophenone

was added to the extraction vessel, and extraction continued for an additional 36 hr. The pentane solution from the first extraction was filtered through a bed of anhydrous magnesium sulfate mixed with anhydrous sodium carbonate; the solution from the second extraction was filtered through the same bed, followed by 1.0 g. of inactive 3,4-dimethylacetophenone to flush out the radioactive material.

The combined filtrates and washings were distilled to remove solvent, an additional 7.0 g. of inactive 3,4-dimethylacetophenone was added to the residue, and distillation continued (using a 30-cm. wire-spiral-packed column) to yield 1.2 g. of material boiling at 31-71° (0.1 mm.). This fraction contained the by-products of the rearrangement, the principal one of which was shown to be camphor by a comparison of its v.p.c. retention time and infrared spectrum with those of an authentic sample. The camphor solidified in the head and condenser during distillation and was remelted with a small flame.

Distillation was discontinued and the column washed down with 1.0 g. of inactive 3,4-dimethylacetophenone. Then 1.1 g. of a mixture of inactive by-products obtained from the rearrangement of inactive fenchone was added to the boiler. Distillation was continued using a 22-cm. heated vacuum-jacketed Vigreux Column equipped with a fractionating head; the fractions were examined by v.p.c. (Column K, 200°) as they were collected. Ten fractions (total weight = 4.4 g.) were taken before

the principal one (13.7 g., 57.8-59° (0.3 mm.)). When as much of the product as possible had been collected, 1.0 g. of inactive 3,4-dimethylacetophenone was added to the residue and distilled to yield 1.1 g. of sample which was combined with the main fraction. Fractions 5-10 were combined and redistilled to yield, in addition to three forefractions, 3.6 g. of acceptably pure material which was added to the main sample (total weight = 18.4 g.), which was then diluted to 20.0 g. with inactive 3,4-dimethylacetophenone.

The 2,4-dinitrophenylhydrazone was prepared in 97% yield by heating on the steam bath for 20 min., 108 mg. (0.729 mmole) of the final diluted product with 10% excess of a 0.15 F stock methanolic solution (0.3 F in sulfuric acid) of 2,4-dinitrophenylhydrazine. The dried product was recrystallized three times from dioxane and vacuum dried; m.p. 256-257° (Kofler block, with some pre-melting at 253°). Duplicate radioactivity analyses gave the value 1.701 ± 0.006 $\mu\text{c/mmole}$. The yield of radioactivity in the rearrangement was 44%.

Degradation of Radioactive 3,4-Dimethylacetophenone

Haloform Reaction of 3,4-Dimethylacetophenone.— The procedure used was an adaptation of that given in Shriner, Fuson and Curtin (39). A sample of the radioactive 3,4-dimethylacetophenone (501 mg., 3.38 mmole) was dissolved in 15 ml. of dioxane, and 5 ml. of 10% sodium hydroxide was added. To the magnetically stirred suspension

was added all at once 23 ml. of a solution prepared by dissolving 10 g. of iodine and 20 g. of potassium iodide in 80 ml. of water. After 1.5 min., sufficient 10% sodium hydroxide (about 2 ml.) was added to react with the excess iodine (the yellow-brown mixture became lemon yellow), and most of the sample was poured into 110 ml. of water. The remaining yellow-brown sticky globules were dissolved in a little dioxane, and a few drops of 10% sodium hydroxide was added to destroy the dark coloration. The solution was added to the main aqueous mixture and refrigerated overnight.

The iodoform was collected and air-dried (586 mg., 44% yield), then recrystallized three times from 95% ethanol and vacuum-dried (149 mg.; m.p. 123° d., Kofler block). Radioactivity analyses in quadruplicate gave 0.810 ± 0.006 $\mu\text{c}/\text{mmole}$ for this material.

The aqueous filtrate from above was evaporated to near dryness on the steam bath under reduced pressure (rotary evaporator); the residue was redissolved in 20 ml. of water, filtered, and acidified with 15 ml. of 10% hydrochloric acid. The resulting precipitate was suction-filtered from the iodine-colored solution, washed well with water and air-dried (221 mg., 44% yield). It was recrystallized three times from 60% (vol.) aqueous acetic acid, but since the product was still cream-colored, it was redissolved in the combined mother liquors and heated with two separate portions of activated charcoal. About 1 ml. of water was added to the hot solution; the 3,4-dimethylbenzoic acid was allowed to crystallize

slowly to yield a clean white product which was collected and dried under reduced pressure (71 mg.; m.p. 165-166°, sealed capillary; lit. (40) m.p. 166.5°). Radioactivity analyses in triplicate gave for the pure material 0.873 ± 0.005 $\mu\text{c}/\text{mmole}$.

3,4-Dimethylphenyl Acetate.— The procedure was adapted from that of Emmons and Lucas (41). Peroxytrifluoroacetic acid was prepared by the dropwise addition (over a period of 1 hr.) of 48.5 g. (0.231 mole) of freshly distilled trifluoroacetic anhydride (38-40°) to an ice-cooled suspension of 6.5 g. (0.19 mole) of hydrogen peroxide (as a 90% solution) in 40 ml. of dichloromethane. The resulting water-clear solution was added dropwise over 1 hr. to 18.5 g. (0.125 mole) of radioactive 3,4-dimethylacetophenone in 160 ml. of dichloromethane containing 83 g. (0.58 mole) of finely powdered disodium hydrogen phosphate; the solvent refluxed from the exothermic reaction, and efficient stirring of the viscous mass was required to keep the reaction under control. The mixture was stirred and heated at reflux for 1 hr. after the completion of addition.

The solids were filtered out with suction and washed with 200 ml. of dichloromethane, and the filtrate and washings were extracted with 75 ml. of 6% sodium carbonate and dried over anhydrous magnesium sulfate. The aqueous layer was washed with a little dichloromethane which was added to the main body of solution; the solvent was removed

by distillation. The crude material was distilled through a 22-cm. heated vacuum-jacketed Vigreux column to yield 0.4 g. of bright yellow forecut (52-59° (0.6 mm.)) and 16.7 g. of pale yellow liquid boiling at 62-65° (0.6-0.7 mm.). Flash distillation of the residue using a semi-micro apparatus afforded an additional 0.8 g. of sample. The infrared spectra of the first two fractions were virtually identical to that of an authentic water-clear sample of 3,4-dimethylphenyl acetate. The spectrum of the third fraction indicated that it was mainly the desired product contaminated by easily detectable impurities. The combined weights of the three fractions represent an 87% yield.

3,4-Dimethylphenol.— A solution of 17.8 g. (0.108 mole) of radioactive 3,4-dimethylphenyl acetate in 150 ml. of anhydrous ether was added dropwise, at a rate sufficient to maintain a moderate reflux, to 4.0 g. (0.11 mole) of lithium aluminum hydride suspended with stirring in 30 ml. of ether. Stirring at room temperature was continued for 1 hr. and 15 min. after the completion of addition. The excess lithium aluminum hydride was decomposed with water and the mixture acidified with 130 ml. of 10% sulfuric acid. The aqueous layer was separated, further acidified with 20 ml. of 10% sulfuric acid and extracted with 40 ml. of fresh ether. The aqueous layer was again acidified with 20 ml. of the dilute acid and continuously extracted with ether for 12 hr.

The combined ether solutions were dried over anhydrous magnesium sulfate and distilled through a 30-cm. wire-spiral-packed column to remove solvent. The boiler contents were transferred to a smaller flask, and distillation was continued with a bath temperature up to 165° to yield 1.5 g. of ethanol (70-77.5°). The residue, which solidified on refrigeration, was recrystallized from n-hexane, and the mother liquors repeatedly concentrated until no more 3,4-dimethylphenol could be obtained; the combined air-dried samples weighed 11.7 g. (89% yield).

3,4-Dimethylphenyl-3,5-dinitrobenzoate.— A portion of the radioactive 3,4-dimethylphenol was recrystallized once more from n-hexane; 104 mg. (0.852 mmole) of the recrystallized material was mixed intimately with 0.25 g. (1.1 mmole) of 3,5-dinitrobenzoyl chloride and heated on the steam bath until most of the mixture had liquified. Pyridine (1 ml.) was added to dissolve the sample completely, and the solution heated on the steam bath for 10 min. The solution was cooled to room temperature, 6 ml. of 5% sodium carbonate solution was added, and the resulting precipitate was collected by suction filtration, washed with water and vacuum dried (131 mg., 49% yield). The sample was twice recrystallized from 95% ethanol (activated charcoal was used in the first recrystallization) and dried for 3 hr. at 60° (< 1 mm.); m.p. 181-182° (Kofler block), with some peripheral melting at 171-174° followed by resolidification (lit. (42) m.p. 181.6°). Duplicate ¹⁴C analyses gave

$0.868 \pm 0.001 \mu\text{c}/\text{mmole}$. Further recrystallization of this derivative would probably have brought the radioactivity into closer agreement with the values for 3,4-dimethylbenzoic acid and 4-methoxy-1,2-benzenedicarboxylic acid (see below). In view of the agreement between the latter two, no further purification and analysis of the 3,5-dinitrobenzoate was carried out.

3,4-Dimethylanisole.— The procedures for the preparation and oxidation of 3,4-dimethylanisole were adapted from those given by King (43). The radioactive 3,4-dimethylphenol (11.5 g., 0.0942 mole) as a solution in 55 ml. of 2 F sodium hydroxide was stirred magnetically and heated to 95° in a 300-ml. flask equipped with two dropping funnels and a reflux condenser. The temperature was maintained at $92\text{--}97^\circ$ during the simultaneous dropwise addition (over a period of 10 min.) of 55 ml. of 2 F sodium hydroxide and 18 ml. (about 14 g., 0.11 mole) of methyl sulfate, and for 30 min. after the completion of addition.

The mixture was cooled to room temperature and extracted with 70 ml. of ether in two portions; the aqueous layer was then extracted continuously with ether for 30 hr. The combined ether solutions were dried over anhydrous magnesium sulfate and distilled to remove the solvent. The crude product was distilled through a 22-cm. vacuum-jacketed heated Vigreux column to yield 0.3 g. of product boiling at $66\text{--}69^\circ$ (5 mm.) and 12.0 g. boiling at $68.5\text{--}69^\circ$ (5 mm.; full vacuum

was used to bring over the last of the product), with 0.3 g. of undistilled residue. The weight of the combined fractions represents a 96% yield.

4-Methoxy-1,2-benzenedicarboxylic Acid.— Eleven grams (0.0808 mole) of the radioactive 3,4-dimethylanisole was suspended in 30 ml. of 10% sodium hydroxide in a 2-l. flask equipped with a stirrer, reflux condenser and dropping funnel. It was heated on the steam bath while a solution of 80 g. (0.51 mole) of potassium permanganate in 1100 ml. of water was added dropwise over 6 hr. Heating was continued for 2.5 hr. after the completion of addition.

The hot mixture was suction filtered and the solids washed with 130 ml. of 1% sodium hydroxide; the combined filtrate and washings (still permanganate-colored) were cooled to room temperature, acidified with 40 ml. of concentrated hydrochloric acid (which destroyed the excess permanganate) and refrigerated overnight. The mixture was filtered to remove 0.2 g. of 2-methyl-4-methoxybenzoic acid; the filtrate was concentrated under reduced pressure on the steam bath (rotary evaporator) until crystallization began (about 200 ml.), and then cooled slowly to room temperature and refrigerated overnight. The precipitate was collected by suction filtration, washed with ice water, and vacuum-dried to yield 12.9 g. of material which, when recrystallized from water, yielded three crops weighing 7.9 g., 1.2 g., and 0.4 g. No more acid could be obtained from the mother liquor, indicating that the original 12.9 g. of precipitate probably contained inorganic salts.

The filtrate was extracted continuously for 30 hr. with ether, and the extract was evaporated to dryness in a stream of nitrogen to yield 2.9 g. of a solid whose infrared spectrum as a mineral-oil mull was similar to that of the recrystallized acid, but which contained an additional broad band at 3500 cm^{-1} . The combined weights of the three recrystallized samples and the residue from the ether extraction represent a yield of 78%. Melting points were not determined since the acid readily forms the anhydride on heating.

A sample of Crop 1 from above was recrystallized twice from ethyl acetate and vacuum-dried overnight at room temperature. Radioactivity assay in quadruplicate showed the activity to be 0.876 ± 0.004 $\mu\text{c/mmole}$.

Brominative Decarboxylation of 4-Methoxy-1,2-benzenedicarboxylic Acid.— The procedure was based on that given by Berman and Price (44) for the decarboxylation of 4-methoxybenzoic acid. Three grams (0.015 mole) of radioactive 4-methoxy-1,2-benzenedicarboxylic acid (from Crop 1 of the above preparation) was dissolved in 30 ml. of 10% sodium hydroxide, and 50 ml. of water was added. The solution was stirred magnetically and heated to about 55° , then 4.8 g. (0.030 mole) of bromine was added dropwise over the period of a few minutes. The resulting turbid solution was heated at $55\text{--}60^\circ$ for 15 min., and acidified while still hot with a solution of 25 ml. of concentrated hydrochloric acid in an equal volume of water. Some carbon dioxide was evolved and a

dense precipitate formed. The mixture was heated on the steam bath for 45 min., and filtered hot to collect the 2,4-dibromo-5-methoxybenzoic acid, which was washed with hot water and vacuum-dried; 1.5 g. (32% yield), m.p. 197-202° (Kofler block) with peripheral melting from 176°. A portion of the acid was recrystallized from 50% aqueous ethanol and twice more from chloroform; m.p. 205° (Kofler block preheated to 195°, lit. (45) m.p. 203°).

Anal. Calcd. for $C_8H_6O_3Br_2$: C, 31.00; H, 1.95; Br, 51.56; neut. equiv., 310. Found: C, 30.92; H, 2.06; Br, 51.60; neut. equiv., 314.

The n.m.r. spectrum of the acid in acetone showed the two ring-proton resonances as well separated singlets, consistent with the structure of 2,4-dibromo-4-methoxyphthalic acid. Duplicate radioactivity analyses of a vacuum-dried sample showed the ^{14}C activity to be 0.0201 ± 0.0002 $\mu c/mmole$.

The original filtrate from above deposited a second crop of crystals when allowed to cool to room temperature; 0.4 g., m.p. 135-165°. The filtrate was then chilled in ice for several hours to precipitate 4-methoxy-5-bromo-1,2-benzenedicarboxylic acid which was collected and dried; 1.5 g., 36% yield. A sample was recrystallized twice from water (it was treated with activated charcoal in the first recrystallization) and vacuum-dried over phosphorous pentoxide; m.p. 201-201.5° (Kofler block

preheated to 195°). The acid forms the anhydride on heating and the melting point depends on the rate of heating. Faltis et al. (46) observed foaming at 192° and melting at 195.5°.

Anal. Calcd. for $C_9H_7O_5Br$: C, 39.30; H, 2.57; Br, 29.05.

Found: C, 39.16; H, 2.49; Br, 29.14.

A potentiometric titration showed a distinct inflection point at one-half the end point. The ring-proton resonances in the n.m.r. spectrum of the acid in methanol appeared as well separated singlets. Both of these observations are consistent with the structure of 4-methoxy-5-bromophthalic acid.

Rearrangement of Camphor

One gram of resublimed camphor was added to 6 ml. (about 11 g.) of 95.5-96.5% sulfuric acid maintained at 90°. Samples were withdrawn periodically, quenched with water and extracted with pentane. The solvent was pumped off under reduced pressure and the residue examined by v.p.c. (Column K, 192°). The vapor-phase chromatogram of the product of rearrangement for 1 hr. is given in Figure 7-B; earlier samples showed the same constituents in different proportions. The main product was designated as carvenone on the basis of the known behavior of camphor in sulfuric acid (4). Carvacrol (2-methyl-5-isopropylphenol) and p-cymene, which might also be formed under the conditions of the rearrangement (24), were examined by v.p.c., but could not be correlated

with any of the unidentified products. Carvacrol apparently reacted with the column packing, since only a few small broad peaks appeared in the analysis of a relatively large sample. It is obvious from a comparison of vapor-phase chromatograms (Figures 7-A and 7-B) that the same mixture of components, in different proportions, is produced in the rearrangements of both camphor and fenchone.

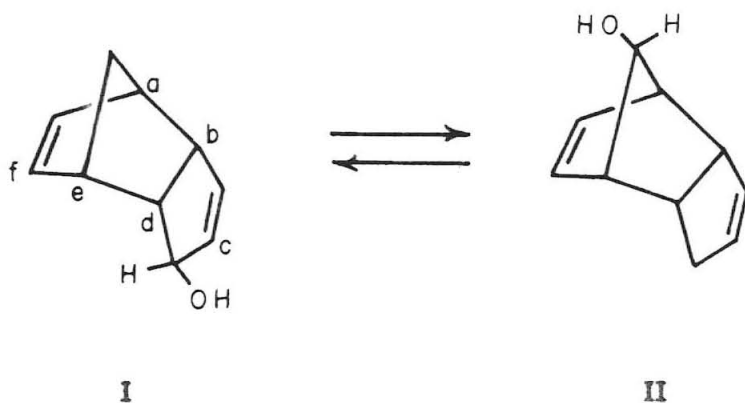
PART II

MECHANISM OF THE DIELS-ALDER REACTION

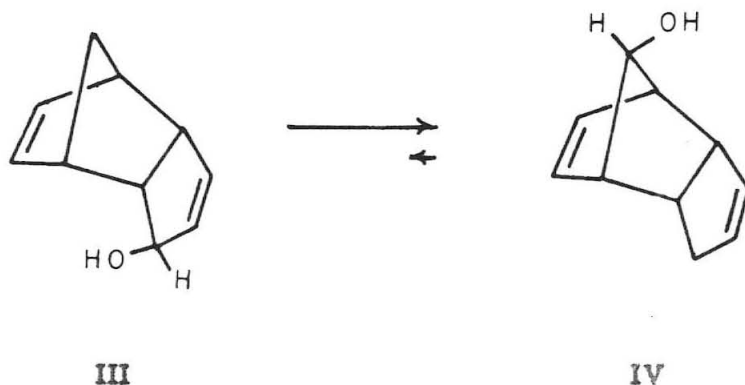
PART II

Introduction

The thermal isomerization of optically active α -1-hydroxy-dicyclopentadiene (I) at 140° yields an equilibrium mixture containing approximately equal amounts of I and syn-8-hydroxydicyclopentadiene (II) (47). The optical activity of I recovered from the mixture is un-

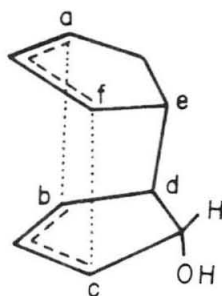


changed from the original value, and the same equilibrium composition is obtained starting with the pure isomer II. Similarly, optically active β -1-hydroxydicyclopentadiene (III) is converted to active anti-8-hydroxy-dicyclopentadiene (IV), the equilibrium in this case lying strongly in



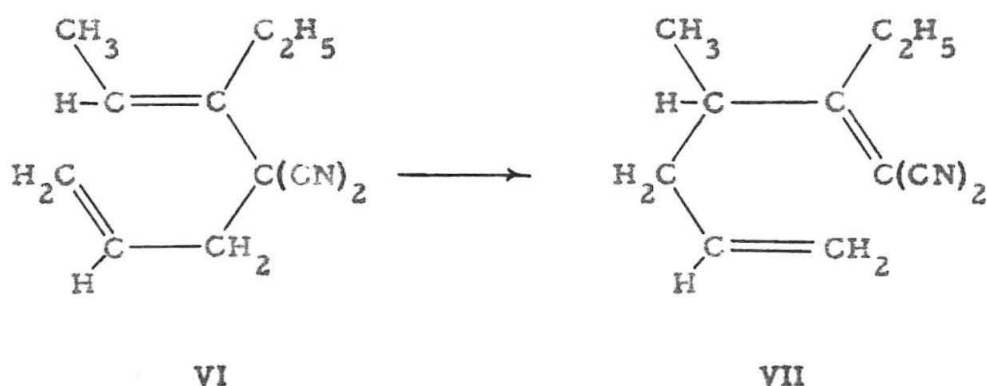
favor of IV. No rearrangement is observed at temperatures substantially below 135°, and above 150° the compounds decompose uncleanly to yield a mixture of products.

To account for the complete geometric and optical stereospecificity of the isomerizations, Woodward and Katz (47) proposed that they were effected by the rupture of bond ab of the dicyclopentadiene skeleton and the formation of a bond between c and f while the bond ed remained intact. At some point in the transformation, the reactant (I, for example) would assume the configuration V in which one bond is being broken at the same time that one is being formed.

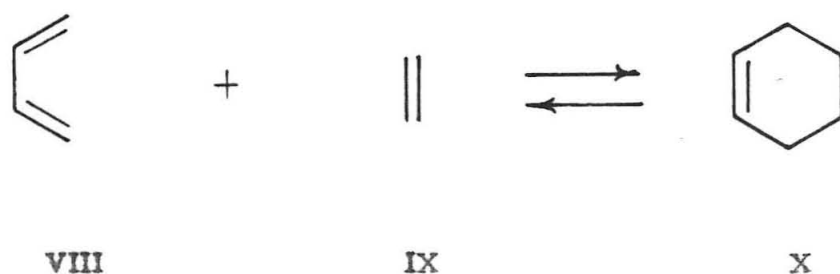


V

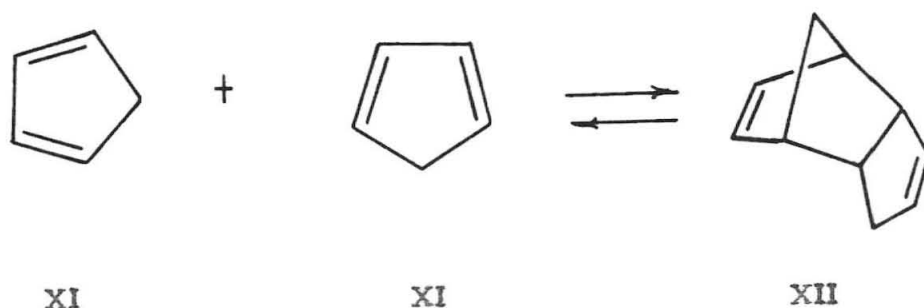
These reactions are interesting as unusual cases of the Cope rearrangement (48), a typical example of which is the thermal isomerization of 1-ethylpropenyl allylmalonitrile (VI) to (1-ethyl-2-methyl-4-pentenylidene)-malonitrile (VII), but they possess an additional significance since the compounds undergoing isomerization are Diels-Alder adducts, which ordinarily cleave thermally into two addends. The



Diels-Alder reaction has been reviewed adequately and repeatedly elsewhere (49), and its mechanism will be discussed in a later section. It may be defined as the reversible thermal addition of a conjugated diene (VIII) and an olefin (IX, known as the dienophile) to yield a cyclo-



hexene adduct (X). A single component may serve both as diene and dienophile, so that the overall reaction is a dimerization as in the addition of cyclopentadiene (XI) to itself to yield dicyclopentadiene (XII).



This dimerization takes place readily at room temperature and the reverse reaction proceeds cleanly at about 150° (50).

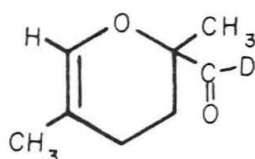
Since the hydroxydicyclopentadienes at the higher temperatures very probably undergo the same kind of dissociation, which in this case is complicated by the instability of hydroxycyclopentadiene, * Woodward and Katz presumed that in the dissociation to give two molecules of addends, one of the bonds was broken first to give species V which then yielded products by the rupture of the second bond. (Species V was identified as occurring at some point on the energy surface for the dissociation reaction but was not defined further as representing a maximum or minimum on this surface.) It was then proposed that all reverse Diels-Alder reactions proceed in a similar manner and consequently, on the basis of the principle of microscopic reversibility (52, 53, 54), ** that the forward Diels-Alder reaction involves some species in which one of the new bonds is fully established while the other is in the process of formation.

Whether or not the isomerizations of the hydroxydicyclopentadienes are related to the Diels-Alder reaction, other Diels-Alder dimers are expected to rearrange in a similar manner, and, indeed, the conversions of 8-ketodicyclopentadiene (55) and a chlorinated derivative (56)

*Hydroxycyclopentadiene has apparently never been isolated as a pure compound. Dissociation in this case yields cyclopentadiene and cyclopent-2-en-1-one (51), the latter presumably arising from the first-formed hydroxycyclopentadiene.

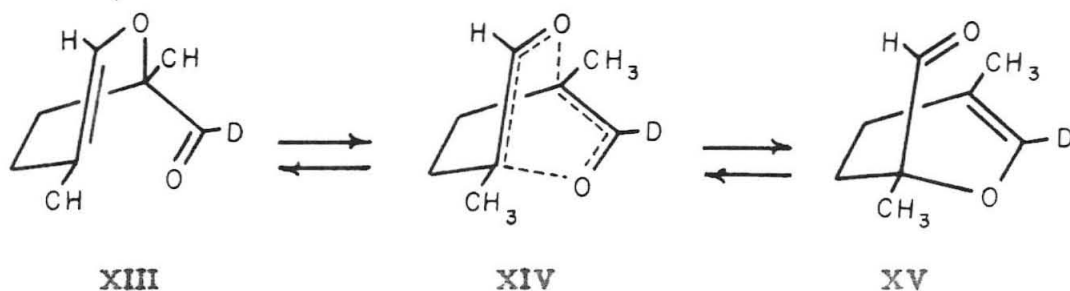
**Which may be stated here as follows: For a reversible reaction, the forward and reverse reactions occur on the same energy surface.

to their respective 1-keto isomers have been interpreted as involving analogs of species V. In the study reported in the following section, optically active methacrolein dimer (XIII)* labeled with deuterium at the aldehyde hydrogen was examined. It should rearrange thermally



XIII

and reversibly through species XIV** (analogous to V) to yield XV, the



overall process converting the aldehyde deuterium to a vinyl substituent

*A structure proof of methacrolein dimer has not been carried out, but the typical behavior of Diels-Alder reactions (cf. Discussion) and the known structures of the closely related dimers of acrolein (57) and methyl vinyl ketone (58) leave no doubt that formula XIII is the correct one.

**The bicyclobutane formulation above is used only to make clear the general character of the transformation which is taking place and should not be taken as a precise description of the geometry of the species involved. A more detailed representation of XIV is given on page 90.

and occurring with retention of optical activity. The extent of rearrangement could be followed by nuclear magnetic resonance (n.m.r.) spectroscopy, since the vinyl and aldehyde proton resonances should appear in widely separated regions of the spectrum and deuterium absorption occurs completely out of the range of proton resonance.

The rearrangement was observed as anticipated (59), with the added feature that the reverse Diels-Alder reaction to yield methacrolein occurred in competition with it.

Experimental Results

The Diels-Alder addition of methacrolein to itself yielded the dimer which was converted to optically active XIII by a Cannizzaro reaction to the corresponding acid, followed by resolution through the brucine salt, conversion of the sodium salt of the acid to the acid chloride with oxalyl chloride, formation of the corresponding N-methyl-N-phenylamide and reduction with lithium aluminum deuteride.

The experimental data for the rearrangement of XIII at its boiling point (171°) are summarized in Figure 1. Methacrolein distilled from the reaction mixture and was condensed at -78°; no other by-products were detected. The optical activity of the rearranged dimer, which represents 99.5% retention of configuration, was determined for a sample twice vacuum-distilled to remove traces of methacrolein which

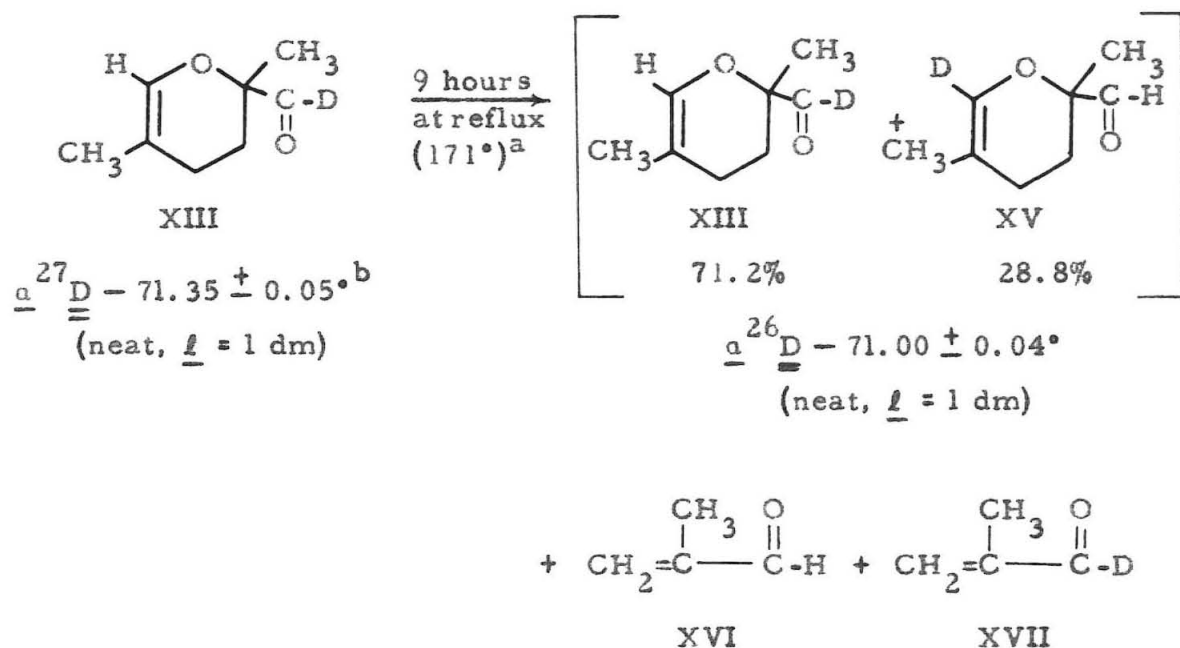


Fig. 1.— Rearrangement of XIII at 171°. ^aThermometer bulb immersed in the boiling liquid; rearrangement proceeded at an inconveniently slow rate at 160°. Hydroquinone (0.8%) was used to inhibit polymerization; nonetheless, 4.1% of polymeric residue was formed. In a sealed tube in the absence of inhibitor, 30% of the starting material was converted to polymer in 7 hours at 180°. Root-mean-square error.

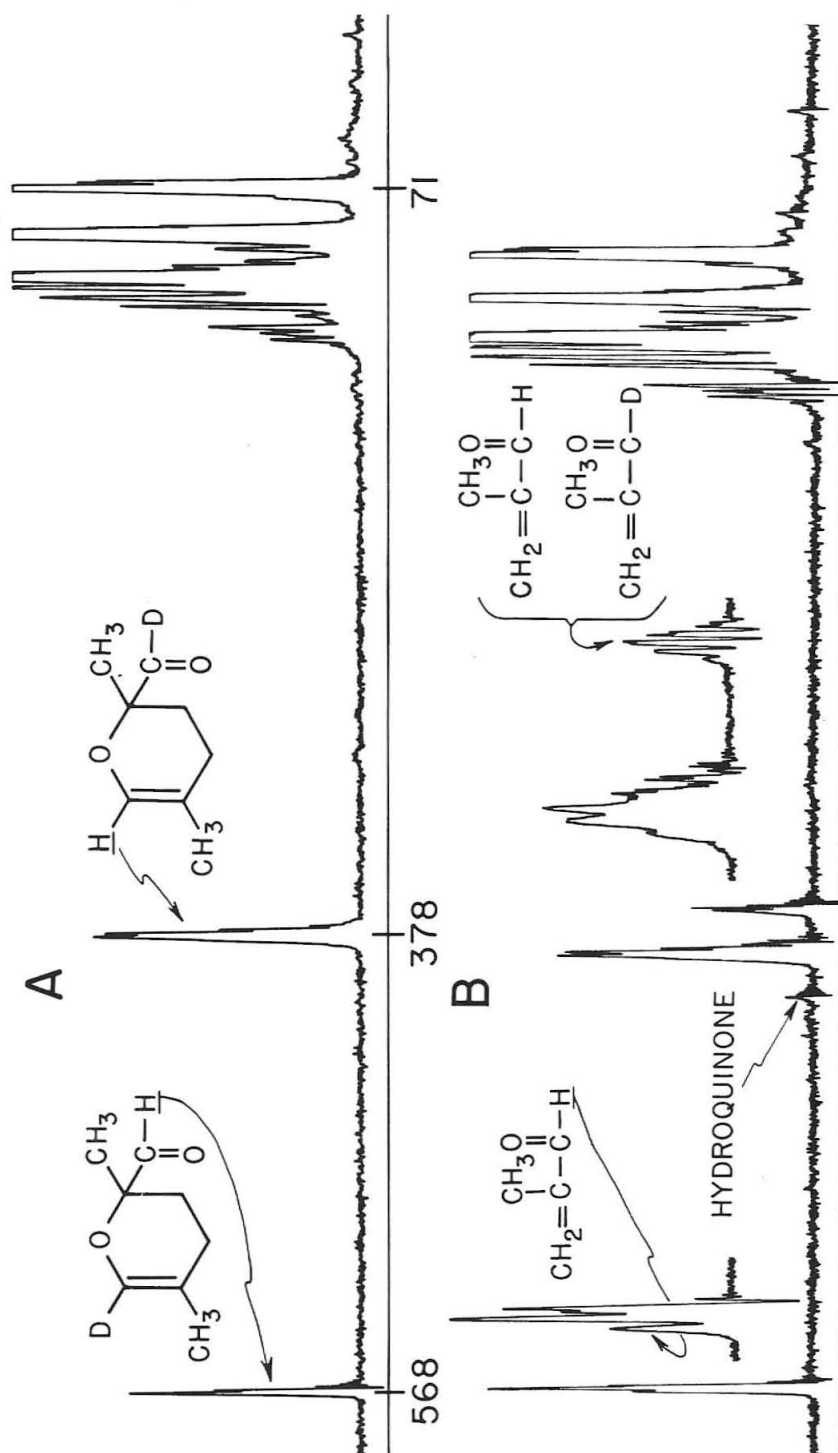


Fig. 2.— Proton n.m.r. spectra at 60 Mc of rearranged dimers. Chemical shifts are in cps from tetramethylsilane ($\equiv 0$ cps) as internal standard. A. Distilled dimer mixture after 9 hours at 171° in an open system. B. Crude product mixture after 7 hours at 180° in a sealed tube. The inset enlargements of the aldehyde and vinyl regions were taken at a reduced sweep rate. One of the vinyl hydrogen resonances of methacrolein is buried under that of the dimer. For comment on the unusual splitting of the dimer aldehyde proton resonance, see D. R. Davis, R. P. Lutz and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 246-7 (1961).

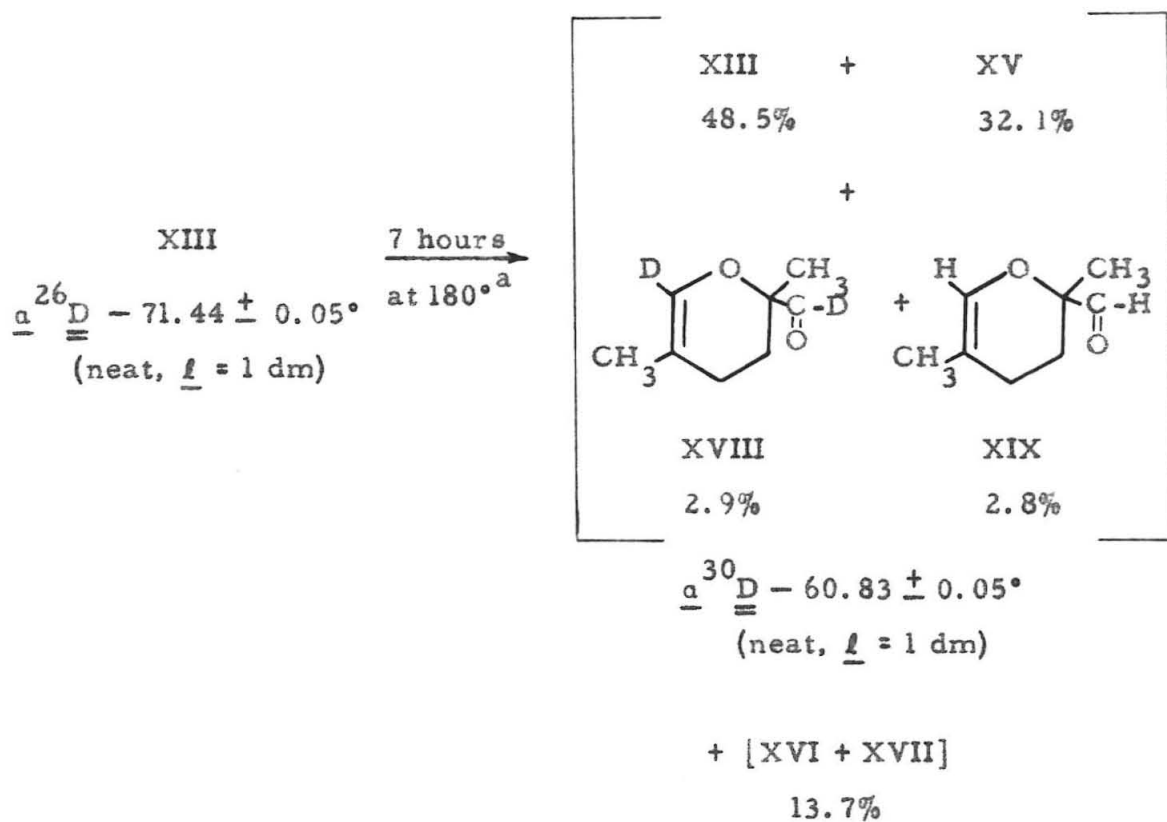


Fig. 3.— Rearrangement of XIII in a sealed tube at 180° . The product distribution is given in mole percent. ^aHydroquinone (0.9%) added; <2.7% of polymeric residue was formed.

remained persistently dissolved. The relative amounts of XIII and XV were determined by electronic integration of the n.m.r. absorption signals of the aldehyde and vinyl protons in the distilled dimer mixture (Fig. 2-A).

A second rearrangement was carried out in a sealed n.m.r. tube; the experimental results are summarized in Figure 3. The relative amounts of rearranged and unrearranged dimers and of methacrolein formed were determined directly in the reaction mixture by n.m.r. spectroscopy (Fig. 2-B). The amounts of dideuterated (XVIII) and undeuterated (XIX) dimers, expected through random recombination of XVI and XVII by a forward Diels-Alder reaction (with a corresponding loss of optical activity) were determined with a mass spectrometer. Their values are slightly below that expected (3.2% each, of the total product) if the only pathway for the observed 14.9% loss of optical activity involves dissociation to methacrolein followed by random recombination.

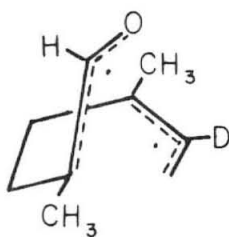
If it is assumed that the non-dissociative rearrangement is a homogeneous first-order reaction, an approximate value for the rate constant k_{-r} , may be calculated using the equation, $\ln \frac{A-B}{A_0} = -2 k_{-r} t$, derived from the expression for opposing first-order reactions (60), in which A and B refer respectively to the concentrations of XIII and XV at time t, and A_0 to the concentration of XIII at time zero. The calculated k_{-r} at 180° is $1.8 \times 10^{-3} \text{ min.}^{-1}$. For the reverse Diels-Alder reaction at

180°, the approximate first-order rate constant, k_d , calculated using the equation $\ln \frac{A}{A_0} = -k_d t$, is $5.2 \times 10^{-4} \text{ min.}^{-1}$. The difference in the two constants represents a difference of free energy of activation of 1.1 kcal. per mole. Details of these calculations are given in Appendix II.

Discussion

The experimental observation of the reverse Diels-Alder reaction occurring in competition with and energetically close to the internal isomerizations provides support for the presumption of Woodward and Katz that the two reactions proceed on the same energy surface. The results do not, however, rigorously exclude the possibility that separate and unrelated energy paths are involved, with the heights of the energy barriers for the two reactions fortuitously close to each other. There is apparently no way to prove unambiguously that the rearrangement represents a partial reverse Diels-Alder reaction.

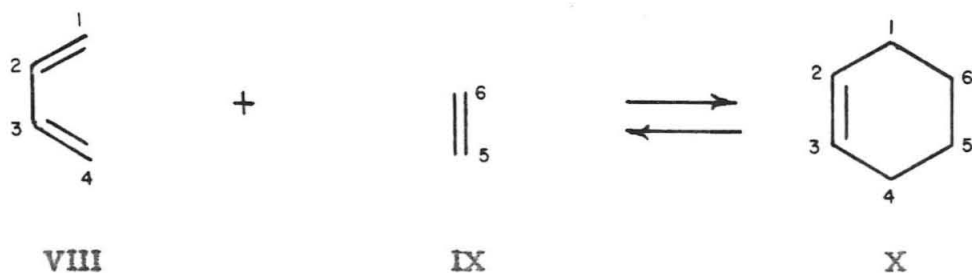
The complete retention of optical activity rules out the intervention, in both the rearrangement and the reverse Diels-Alder reaction, of a diradical intermediate such as XX (cf. p. 91) with a sufficiently long lifetime to permit racemization



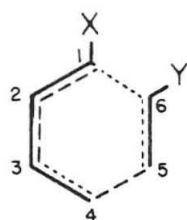
XX

These findings may now be incorporated with other evidence in a general discussion of the mechanism of the Diels-Alder reaction as it is understood at present. It should be noted at the outset that the mechanism is still very much open to debate and that the following survey leads to no all-embracing conclusion. But if, after examining evidence which is more or less universally valid or diagnostic mechanistically, it is not possible to reach any firm positive conclusions except the most obvious ones, it is occasionally possible to make a convincing statement about what the path of the Diels-Alder reactions does not involve.

One-Step and Two-Step Mechanisms.— The traditional views concerning the formation of the adduct (X) from the diene (VIII) and dienophile (IX) may be classified in their extremes as one-step and



two-step mechanisms. In the former (61), it is supposed that both of the two new bonds of the adduct are formed simultaneously in the rate-determining step, involving a transition state, symbolized by XXI, having a steric configuration similar to that of the product molecule and occupying the position indicated in Figure 4-A, a representation of the energy profile for a one-step reaction. The distinction between a symmetrical and an unsymmetrical one-step mechanism is not ordinarily made, but in the reaction of unsymmetrically substituted components, the hybridization changes which represent bond formation (from sp^2 to sp^3 at the centers 1, 4, 5, and 6) may very well have occurred to a different extent in a transition state symbolized by XXII.



XXII

According to the two-step formulation, only one of the bonds is formed in the rate-determining step, leading to what is frequently represented as an open-chain diradical intermediate (XXIII) (62) which occupies a minimum position on an energy profile such as that shown in Figure 4-B. In discussions of the two-step mechanism, the diradical intermediate is assumed to be in the electronic triplet state, but presumably it could just as well be a singlet (61a).

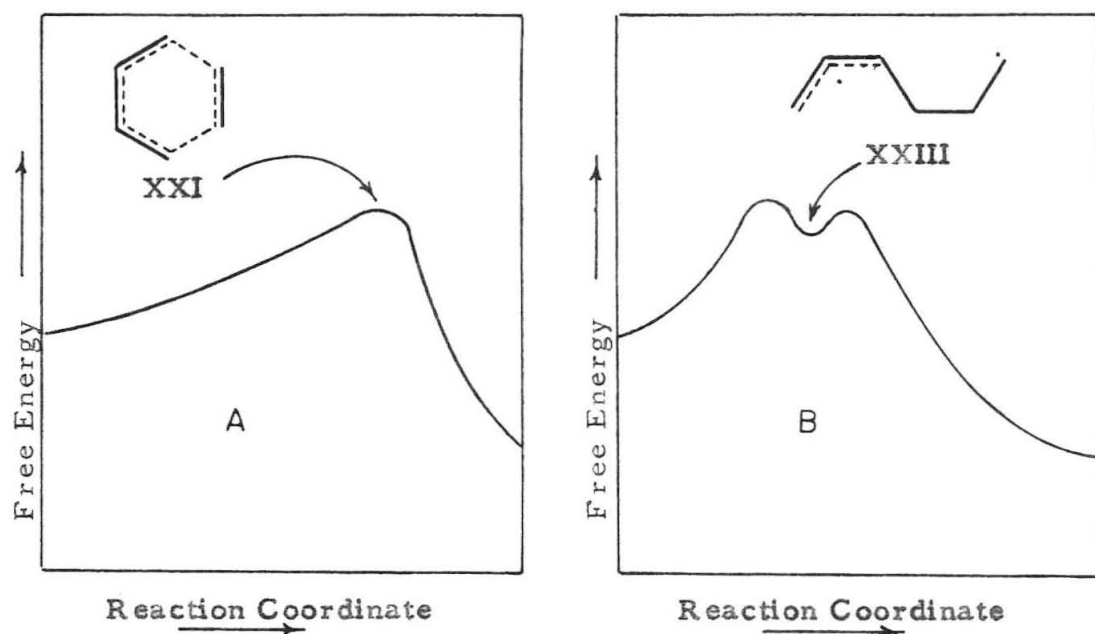


Fig. 4.— Possible energy profiles for the Diels-Alder reaction. The direction of the reaction coordinate represents the forward reaction. The adduct is placed below the addends on the energy scale to accord with the observed exothermicity of the forward reaction (50). A. One-step mechanism. The position of maximum energy is shown displaced to the right of center, since Arrhenius pre-exponential factors for the forward and reverse reactions (referred to in the text) indicate that if the reaction is one-step, the transition state has a geometrical form resembling that of the adduct. This conclusion violates the Hammond postulate (63), which states (as one of its applications) that the transition state for a highly endothermic reaction (a condition met by many reverse Diels-Alder reactions (50)) is expected to resemble the product (in this case, the addends). B. Energy profile for a two-step mechanism. The implications of pre-exponential factors are less clear in this case and the transition state is drawn in the conventional position (63).

Kinetic Evidence; Rate Laws and Activation Parameters.—

Simple rate evidence may be accommodated by either picture. The rates of forward Diels-Alder reactions are usually first order with respect to each component, indicating that both take part in the rate-determining step, and the reverse reactions are first order with respect to the adduct (49e). Activation energies range from 8.0 kcal. per mole for the reaction of benzoquinone and cyclopentadiene in benzonitrile solution (64) through the typical values of 16.0 - 17.7 kcal. per mole for the dimerization of cyclopentadiene in the gas and liquid phases and in various solvents, to 22.0 kcal. per mole for the gas-phase addition of crotonaldehyde to butadiene (50). For the reverse reaction, activation energies from 29 to 35 kcal. per mole, respectively, have been observed for the dissociations of the benzoquinone-cyclopentadiene adduct in benzene solution and of dicyclopentadiene in the gas phase (50).

Arrhenius pre-exponential factors for the forward reaction are consistently low. Typical values of $\log_{10} A$ (A expressed in $l./mole\text{-}sec.$ for all values quoted for the forward reaction) range from about 4.0 to 7.5, observed for the reaction of benzoquinone and cyclopentadiene in carbon disulfide and acetic acid solutions, respectively (50). The values represent very large negative entropies of activation ($\log_{10} A = 4.7$, $\Delta S^\ddagger = -39$ e. u. for the reaction of maleic anhydride with dimethylantracene (65)) and indicate either a highly improbable electronic transition or a severely restricted geometry of the transition state

relative to starting materials (66). The pre-exponential factors for the reverse Diels-Alder reaction (typically, $\log_{10} A$ (A expressed in sec.^{-1}) = 12.1 and 13.1, respectively, for the dissociations of the α -naphthaquinone-cyclopentadiene adduct in benzene solution, and dicyclopentadiene in the gas phase (50)) are in the same range as those observed for a large number of homogeneous unimolecular decompositions (67) and are interpreted as implying no change in electronic multiplicity (50) or significant change in geometry (49e) in forming the transition state from the adduct.

Either mechanistic picture can accommodate the low factors of the forward reaction, but the one-step process more easily rationalizes those of the reverse reaction. If indeed the one-step formulation is the correct one, the implied lengths of the partial single bonds in a transition state such as XXI are sufficiently short to insure the singlet as being the only energetically feasible electronic state.

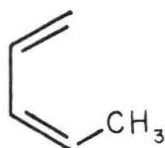
Solvent Effects.— Solvent is often assumed to have little effect on the Diels-Alder reaction (47), but examples of substantial solvent-induced changes in activation parameters have been observed. Increases in solvent polarity promoted the reaction of benzoquinone with cyclopentadiene (64), but retarded the addition of maleic anhydride to anthracene (65). The change in $\log_{10} A$ for the addition of benzoquinone to cyclopentadiene in two different solvents was cited above. More and almost unbelievably dramatic effects were found in the reaction of diphenyliso-

benzofuran with acrylonitrile (68); in chloroform, $\log_{10} A = 2.2$ and $\Delta E^* = 5.7$ kcal. per mole, whereas in carbon tetrachloride $\log_{10} A = 14.5$ (an astoundingly high pre-exponential factor for the forward Diels-Alder reaction, considerably higher than the next highest value (9.6)) and $\Delta E^* = 22$ kcal. per mole. The effects could not be correlated with either the dipole moments or the dielectric constants of the large number of solvents studied. It was found that a change in temperature could reverse the relative effectiveness of two solvents in promoting the reaction. (In the above study, it was not clearly established that complex formation was not a complicating side reaction.)

Quite recently Berson and Mueller (69) studied the effect of solvent on the relative activation parameters for the formation of the exo and endo isomers (refer to the section on stereochemistry) in the reactions of cyclopentadiene with methyl acrylate and with methyl methacrylate. In general a change to more polar solvents reduced the relative activation energies for endo with respect to exo addition, but seemed to favor the exo product on the basis of changes in the pre-exponential factors. (A more thorough study (70) has since shown that the effect of solvents on the pre-exponential factors was more or less random.)

Effect of Substituents.— The effect of substituents on the reaction rate has not been thoroughly examined. Steric factors are certainly important, as shown by the lack of reactivity of maleic anhydride

with cis-piperylene (XXIV) compared to a facile reaction with the trans isomer (XXV) (71). It is usually assumed (49e) and generally true that



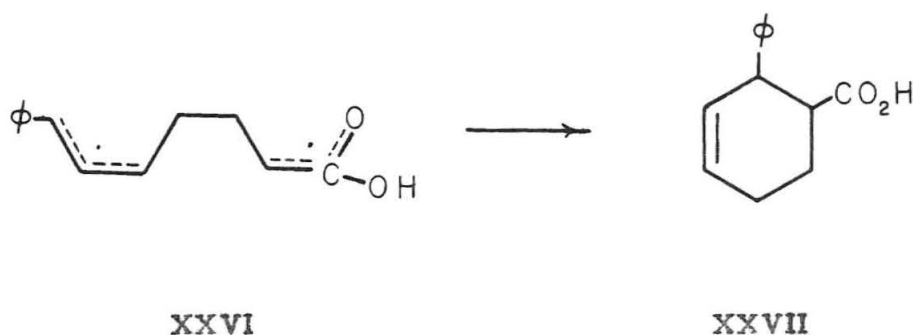
XXIV



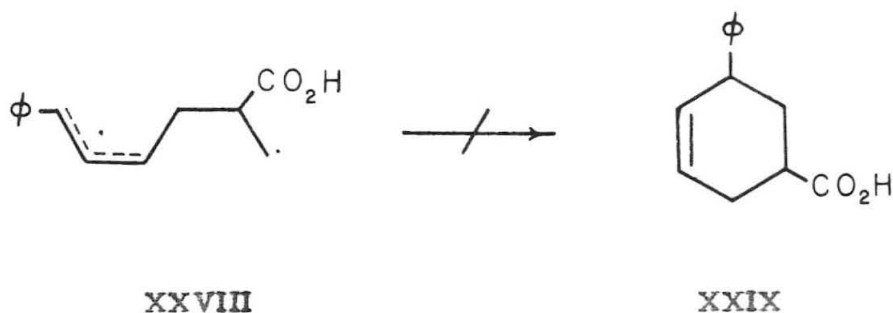
XXV

electron-donating substituents on the diene and electron-withdrawing substituents on the dienophile promote reaction. In the reactions of p-substituted 1-phenylbutadienes with maleic anhydride, the rates increased with the increasing capacity of the para substituent to function as an electron donor, in the order $\text{NO}_2 < \text{Cl} < \text{H} < \text{CH}_3 < \text{OCH}_3$ (rate constant ratios at 25° were $k_{\text{NO}_2}/k_{\text{H}} = 0.23$, $k_{\text{Cl}}/k_{\text{H}} = 0.59$, $k_{\text{CH}_3}/k_{\text{H}} = 1.1$, $k_{\text{OCH}_3}/k_{\text{H}} = 2.7$) (72). A series of p-substituted *N*-phenylmaleimides showed the following decreasing order of dienophile reactivity toward 6,6-diphenylfulvene: $\text{NO}_2 > \text{Cl} > \text{COCH}_3 > \text{CO}_2\text{H} > \text{I} > \text{C}_6\text{H}_5 > \text{H} > \text{CH}_3 > \text{OCH}_3 > \text{N}(\text{CH}_3)_2$ (73). However, in a series of Diels-Alder additions in which acrolein served as the diene component, high yields of adducts were obtained with dienophiles possessing electron-donating substituents (e.g., 84% with methylvinyl ether) whereas those with electron-withdrawing groups reacted in low yield (e.g. 5% with α -methylacrylonitrile) (74a). There was thought to be a positive correlation between yield and reaction rate of adduct formation.

Substituents have an effect on the product composition which may be generalized by the statement that the isomer usually observed is the one predicted on the basis of the most stable diradical intermediate (74). For example, the most stable intermediate expected in the reaction of 1-phenylbutadiene and acrylic acid is XXVI to give the observed product XXVII (75), rather than intermediate XXVIII or some



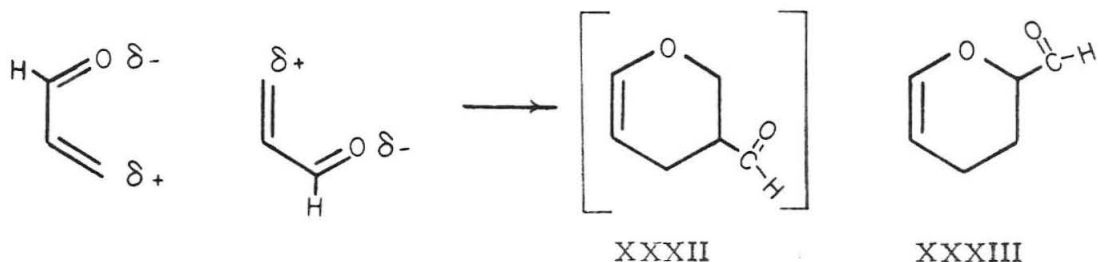
other to give XXIX. One exception to this generalization, among others (74b), is the reaction of methyl acrylate with 2-phenylbutadiene to yield



XXX as a minor product along with the "correct" adduct, XXXI (76).



As a whole, substituent effects favor a two-step over the extreme (symmetrical) one-step mechanism, but any advantage possessed by the two-step mechanism applies equally well to the unsymmetrical one-step picture. Ground-state polarizations which might be expected to influence the direction of addition through a symmetrical one-step process usually lead to an incorrect prediction of products. Polar forces in the dimerization of acrolein should favor XXXII over XXXIII, but only the latter is formed (57)..



Isotope Effects.— No carbon isotope effect (77) was found in the Diels-Alder addition of β -nitrostyrene- α - ^{14}C to 2,3-dimethylbutadiene (78). The reason for the absence of effect is not apparent. The bonding to the isotopically substituted carbon atom is undoubtedly altered in the transition state relative to the ground state, so an isotope effect is anticipated.

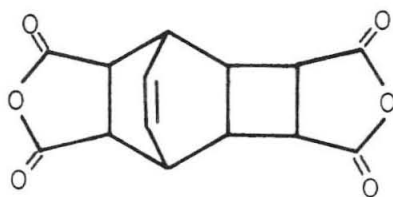
Catalysis.— The effect of catalysts is not clearly established. Several forward Diels-Alder reactions, including the dimerization of cyclopentadiene, have been found to be acid-catalyzed (with the catalytic activity increasing with acid strength) whereas others were catalyzed by phenols (the catalytic activity of the phenols decreased with

increasing acid strength) (79). Lewis acids such as aluminum chloride, stannous chloride, boron trifluoride, ferric chloride and titanium tetrachloride appear to be general catalysts in those cases where they induce no undesirable side reactions (80, 81). Aluminum chloride, for example, when present in equimolar amounts with the reactants, caused an estimated 200,000-fold increase in the reaction rate of anthracene with maleic anhydride (80). Catalysis was observed in the reactions of the simplest diene, butadiene, with a number of dienophiles (81).

The relevance of the catalyzed reactions to the mechanism of the uncatalyzed Diels-Alder reaction is not clear, particularly since a careful comparison of products in the two cases has not been made where more than one isomer might be formed. It is quite conceivable that the catalyzed reactions proceed by a completely unrelated mechanism. The Lewis acid may form polar complexes with appropriately substituted dienophiles, such as maleic anhydride, which then react rapidly with the diene. Alternatively, the initial interaction may be with the diene. Anthracene rapidly forms the positive ion radical by the direct transfer of an electron to aluminum chloride (82), and a number of diphenylpolyenes, including 1,4-diphenylbutadiene, form dipositive ions by electron transfer to titanium tetrachloride (83). Electron-transfer complexes in which the dienophile serves as electron acceptor have been proposed to account for catalysis by phenols (79).

Analogous charge transfers have in fact been postulated as leading to (ion-radical)-pair intermediates in the uncatalyzed Diels-Alder reaction (84), and the formation of complexes from such typical Diels-Alder addend combinations as maleic anhydride with piperylene or isoprene has been verified experimentally (85). However, the fact that molecular complexes usually have small negative heats of formation (86) makes them energetically inappropriate models for the transition state of the uncatalyzed Diels-Alder reaction.

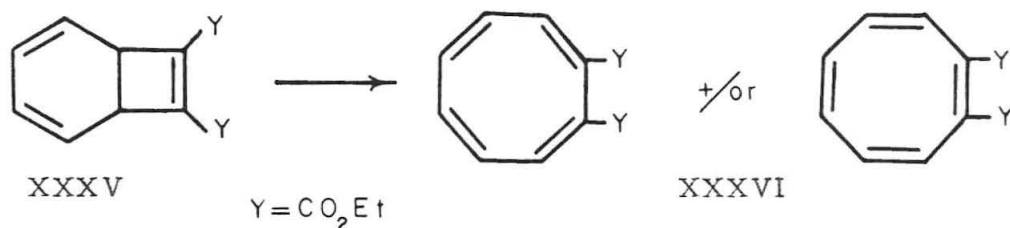
Although the simple expedient of shining an ultraviolet lamp on a solution of Diels-Alder addends usually has no effect (87), some examples of photocatalysis have been observed. The reaction rate of anthracene with maleic anhydride in dioxane solution to yield the normal adduct is increased by light of wave length 3650 \AA (88), and maleic anhydride undergoes a photocatalyzed addition to benzene (89) to yield XXXIV (whose stereochemistry is not yet fully elucidated (90,91)). The



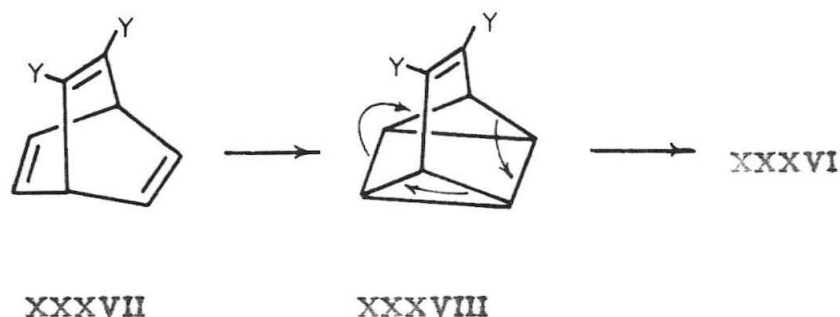
XXXIV

latter case may involve an initial photocatalyzed addition to form the four-membered-ring adduct followed by an uncatalyzed Diels-Alder

reaction. This explanation is made more probable by the observation that the photocatalyzed addition of diethyl acetylenedicarboxylate to benzene yields a substituted cyclooctatetrene (XXXVI) (92) which could result from the isomerization of an initially formed cyclobutane adduct (XXXV).



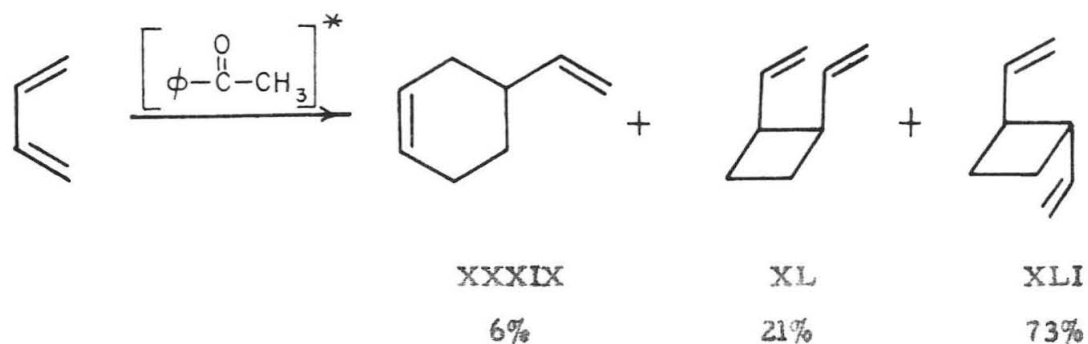
However, the isomerization of a first-formed Diels-Alder adduct (XXXVII) could also lead to the substituted cyclooctatetrene* either directly or through an intermediate such as XXXVIII.



It is perhaps especially significant to the mechanism of the Diels-Alder reaction** that the dimerization of butadiene, which gives predominantly the Diels-Alder adduct, 4-vinylcyclohexene (XXXIX),

*As pointed out by Mr. George Whitesides of this laboratory.
 **Suggested by Professor George S. Hammond.

when carried out thermally (93), yields principally the cis- and trans-1,2-divinylcyclobutanes (XL and XLI) (94) when the reaction is induced by acetophenone in the triplet state (95). The induced reaction very



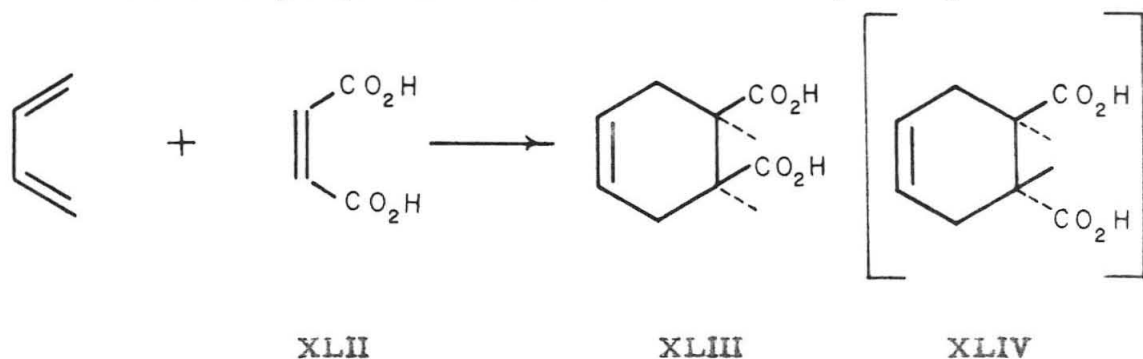
probably involves a triplet diradical intermediate, and the fact that the Diels-Alder adduct is not favored under these conditions argues against the participation of a similar intermediate in the thermal Diels-Alder reaction.

(Competition between cycloadditions to give Diels-Alder adducts and substituted cyclobutanes brings up the unresolved question of the relation of the mechanisms of these two processes (96). Examples of significant competitive formation of cyclobutanes in the thermal Diels-Alder reaction are rare; apparently the only instances which are not special cases are the reactions of butadiene to give both four- and six-membered-ring adducts with perfluoropropene, perfluoroacrylonitrile and 1,1,2-trifluoro-4-bromobut-1-ene (97).)

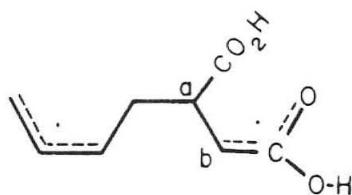
Effect of Pressure.— The Diels-Alder dimerization of isoprene is strongly accelerated by pressure (62c). Interpretation of the effect

is ambiguous, however, and from the same data it is possible to conclude that the transition state is non-cyclic, leading to an open-chain diradical (62c), or, diametrically opposed, cyclic as in the one-step mechanism (98).

Stereochemistry.— The stereochemistry of product formation has been generalized by two empirical rules (99) called (1) the rule of cis addition and (2) the principle of maximum accumulation of unsaturated centers. The first states that the stereochemical relationships of substituents on the dienophile are maintained in the product. For example, the reaction of maleic acid (XLII) with butadiene yields the isomer XLIII but not XLIV (99a). This rule is the most firmly held generalization



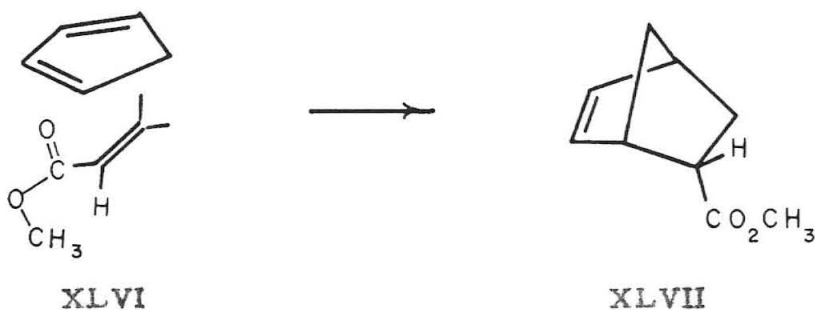
concerning the Diels-Alder reaction and apparently no exception to it is known. It is readily rationalized by the one-step mechanism, but imposes a restriction on the two-step mechanism by requiring that the lifetime of the intermediate (such as XLV) be so brief that rotation around bond ab



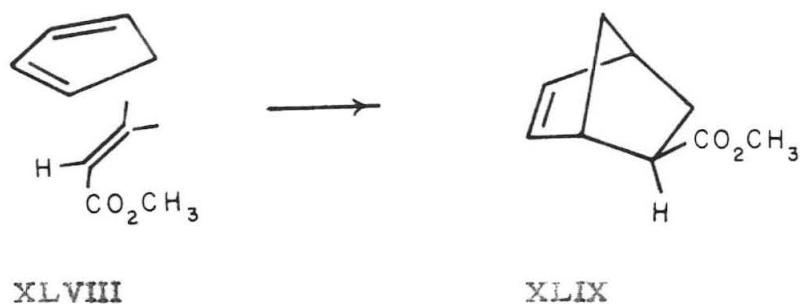
XLV

cannot take place before formation of the second bond.

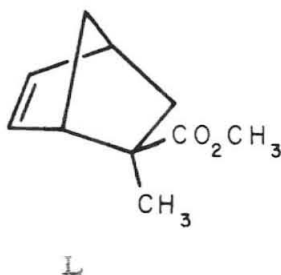
The second principle may be stated as follows: if there are two possible modes of combination which could lead to different configurations of the product, that mode is favored which results from the maximum accumulation of unsaturated centers in the presumed transition state. To illustrate, the reaction of cyclopentadiene with methyl acrylate should yield the endo product (XLVII) from a species such as XLVI which permits some interaction of the unsaturation electrons of the carbonyl group with those of the diene, rather than the exo isomer



(XLIX) from XLVIII, where the interaction is not possible. Numerous



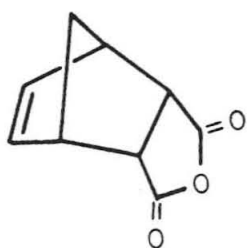
exceptions to this principle are known (100), however, as, for example, the reaction illustrated above; both the exo and endo isomers are formed as kinetically controlled products (101). Furthermore, in the reaction of cyclopentadiene with methyl methacrylate, the relative activation energies actually favor the exo isomer (L) by 0.71 kcal. per mole (101).



Rearrangements of Diels-Alder Adducts.— Some recent investigations have focused on the behavior of Diels-Alder adducts when subjected to the conditions of the reverse reaction, as illustrated by the rearrangements of the hydroxydicyclopentadienes and labeled

methacrolein dimer which have been discussed. The endo adduct, LI, exclusive* product of the addition of maleic anhydride and cyclopentadiene, also rearranges thermally by an internal path, which may represent a partial reverse Diels-Alder reaction, to the thermodynamically more stable exo adduct (LII) (103). The internal route was demonstrated by rearranging ^{14}C -labeled (in the maleic anhydride portion) endo adduct in the presence of inactive maleic anhydride. The amount of radioactivity in the exo adduct showed that about 50% of the reaction was internal while the rest involved dissociation into kinetically free maleic anhydride and cyclopentadiene followed by recombination. The internal isomerization could not involve a caged aggregate which collapsed to yield the exo (or endo) compound before the addends were able to diffuse apart, since the measured rate of the addition reaction was too slow by six to nine powers of ten to be diffusion-controlled (104). It was proposed (104) that if the internal reaction represented a partial reverse Diels-Alder reaction, it involved a high-energy complex, with both bonds between the maleic anhydride and cyclopentadiene fragments weakened, which occupied a minimum position on the reaction coordinate as would the intermediate of a two-step Diels-Alder reaction. It was recognized that the isomerization could also proceed on an energy surface different from that of the Diels-Alder reaction. The mechanism of the

*In a recent study of this reaction, 1.4% of the exo adduct was observed (102).



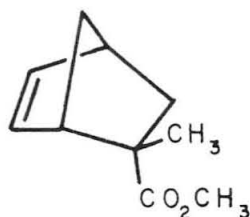
L I



L II

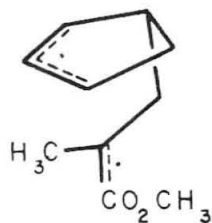
internal isomerization is currently under investigation in these laboratories by Mr. John Baldwin.

Two other Diels-Alder adducts which could conceivably rearrange by an internal route did not do so. Conversion of the optically active exo adduct (L) of cyclopentadiene and methyl methacrylate to the endo isomer (LIII) occurred with complete loss of optical activity



LIII

(74b, 101), indicating that the reaction took place by dissociation to the kinetically free addends followed by recombination. Rotation about bond ab of a possible diradical intermediate such as LIV (or a similar species

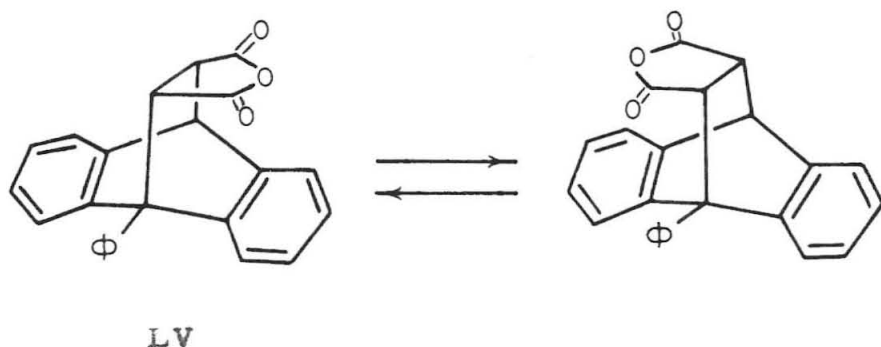


LIV

proposed in the next section) would have yielded the optically active endo compound. The result is actually not unexpected, since a similar rotation if it occurred in an intermediate of the forward Diels-Alder reaction would lead to a loss of stereospecificity which is not observed

(cf. the rule of cis addition, p. 77).

Racemization of the optically active adduct (LV) of maleic



anhydride and 9-phenylanthracene might proceed by an intramolecular process through a complex such as that postulated for the endo-exo isomerization of the cyclopentadiene-maleic anhydride adduct. However no intramolecular mechanism was observed; the rates of loss of optical activity and exchange with ^{14}C -labeled maleic anhydride were identical to the rate of dissociation measured spectrophotometrically (104).

Recent Mechanistic Proposals.— Woodward and Katz have made what is perhaps the most explicit proposal to date concerning the mechanism of the Diels-Alder reaction (47). It is based on the presumption that the rearrangements of the α - and β -l-hydroxydicyclopentadienes represent partial reverse Diels-Alder reactions and, consequently, that the forward Diels-Alder reaction involves some species in which one of the bonds is fully established while the other is in the process of formation (cf. Introduction, p. 56). This mechanism may now be

examined in more detail in the light of the additional evidence presented.

It is stated as follows:

"(1) The diene assumes, if it does not already have, the quasi cis conformation (LVI).



LVI

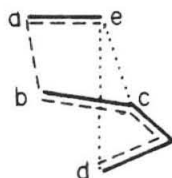
(2) The rate-controlling process consists in the formation of a single bond between one terminus of the diene system and one of the unsaturated centers of the olefin. Accordingly, the diene and olefin approach one another initially in parallel planes, orthogonal to the direction of the bond about to be formed (cf. LVII).



LVII

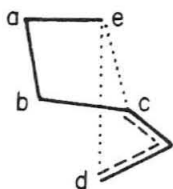
(3) Conformational specificity about the newly-forming bond is determined by secondary attractive forces involving the electrons not directly associated with the primary bonding process (cf. LVIII).^{*} Thus, as electrons at c, d, and e are progressively freed of their involvement with their former partners at a and b, attractive electrostatic, electrodynamic, and even to some extent exchange forces (dotted lines ed and ec in LVIII) stabilize the conformation shown as compared with other a priori available alternatives.

^{*}Solid, dashed and dotted lines represent, respectively, σ bonds, partial bonds and secondary attractive forces.

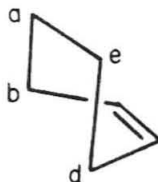


LVIII

(4) After passage of the barrier, formation of the single bond ab is first completed (cf. LIX) and the reaction proceeds to its conclusion with the relatively facile construction of a second full bond at ed (LX)."



LIX

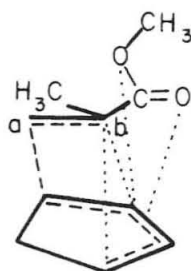


LX

This scheme accounts satisfactorily for the empirical generalizations discussed in the foregoing sections. It meets with the requirement of stereochemical rigidity in the transition state but allows the same substituent effects which would be predicted using the diradical intermediate as a model. It is in fact very close conceptually to an unsymmetrical one-step mechanism, the major difference being the substitution of secondary attractive forces for partial bonds. Secondary attractive forces come into play simultaneously with the inception of formation of the first bond and exist at all stages from the

ground state to the transition state; a partial bond would behave in the same way. Perhaps the biggest distinction between the two pictures is that use of secondary attractive forces allows for the possibility of a second transition state, whereas a symmetrical one-step mechanism, by definition, possesses only one transition state. Leaving definition aside, however, it is possible to conceive of a second energy barrier involving geometrical reorientation in a species possessing two partial bonds (a partial bond between two approaching centers being defined as a change in hybridization at these centers from sp^2 to sp^3 ; presumably the centers at which secondary attractive forces originate are still sp^2).

According to Woodward and Katz's model, secondary attractive forces, which account for the principle of maximum accumulation of unsaturated centers, would favor formation of the endo adduct from transition state LXI for the addition of methyl methacrylate to cyclopentadiene. As has been discussed (cf., p. 79), both the endo and

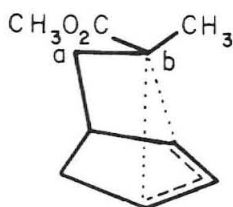


LXI

exo products are formed, with the exo actually favored and the exo-endo ratio dependent on solvent. In this case, the secondary attractive forces

(or whatever forces are responsible for the principle of maximum accumulation of unsaturated centers) are overshadowed by other factors including interaction with solvent.

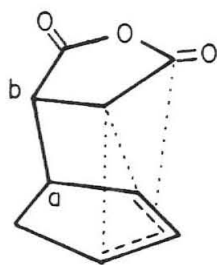
Secondary attractive forces would seem to allow rotation about bond ab of species LXII, presumably involved in the dissociation of the exo adduct of methyl methacrylate and cyclopentadiene. The fact that



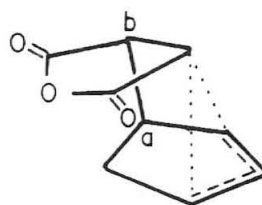
LXII

such rotation is actually not observed (cf., p. 82) prompted Berson, Remanick and Mueller (74 b, 101) to suggest that these forces could more appropriately be designated as partial bonds.

The internal endo-exo isomerization of the cyclopentadiene-maleic anhydride adduct is not readily rationalized as a partial reverse Diels-Alder reaction by Woodward and Katz's model, which predicts the array LXIII in the reverse reaction. Conversion to the corresponding LXIV for exo addition cannot take place without at some point breaking bond ab. If it is assumed that the isomerization is on the path of the reverse Diels-Alder reaction and that in fact a mechanism such as



LXIII



LXIV

Woodward and Katz propose is the correct one, the energy profile for this particular reaction might resemble Figure 5, with the minimum representing a high-energy complex from which either LXIII or LXIV may be formed, the activation energy for exo addition being higher than that for formation of LXIII.

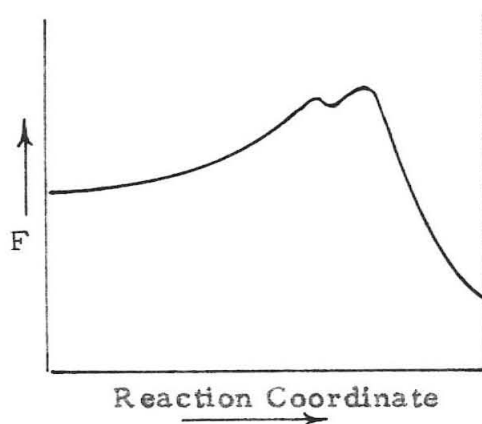


Fig. 5

The rearrangement of optically active deuterium-labeled methacrolein dimer with competing formation of methacrolein by the reverse Diels-Alder reaction is of course in complete accord with the

theory of Woodward and Katz. The rearrangement very probably proceeds through species LXV; assuming that it actually takes place on the energy surface for a partial reverse Diels-Alder reaction, LXV could represent an intermediate occupying the position indicated in Figure 6. The energy profile for the rearrangement itself would then be represented by Figure 7. It is entirely possible, however, that

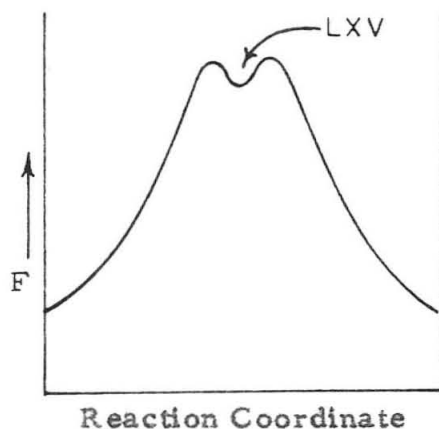


Fig. 7

species LXV occurs at some point before the transition state of a one-step reverse Diels-Alder reaction (cf. Fig. 4-A), so that the energy profile for the rearrangement would possess a single maximum.

If it is argued that the rearrangement occurs on a separate energy surface from that of the Diels-Alder reaction, it is necessary to maintain that the excess energy in the bond undergoing rupture in the rearrangement must be redistributed in the molecule before an additional small increment of free energy may be incorporated to effect

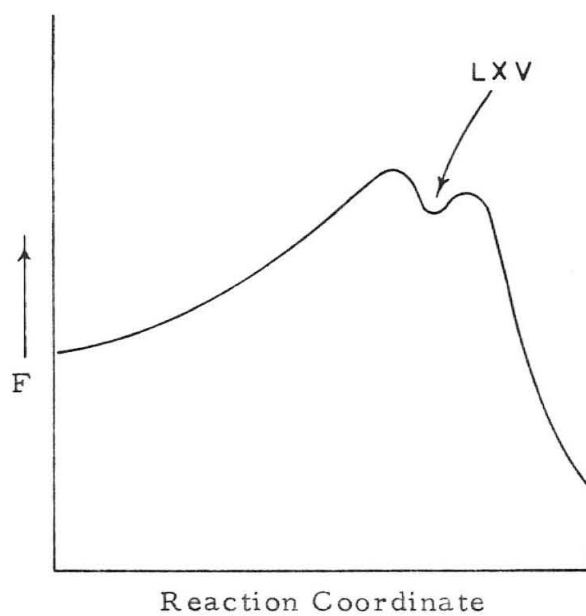
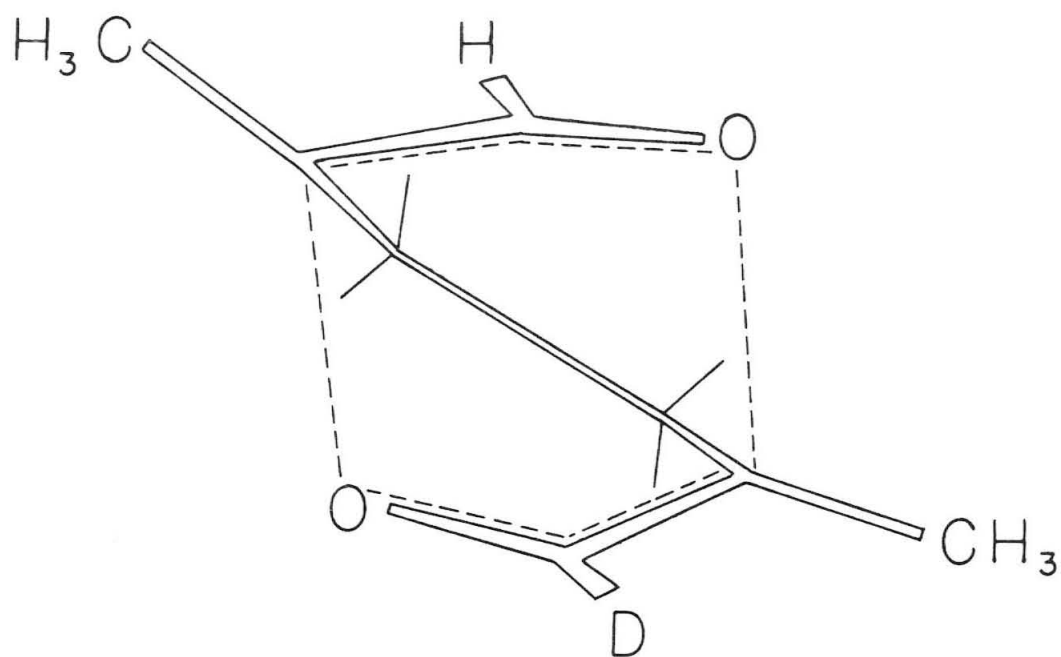
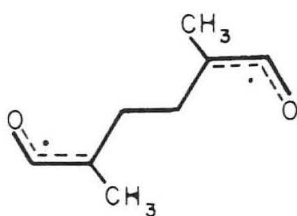


Fig. 6.— The difference in the heights of the two energy barriers at 180° is the 1.1 kcal. per mole observed (cf. p. 63).

complete dissociation, or that a molecule activated for rearrangement must return to the ground state before it can be activated for the reverse Diels-Alder reaction.

It may also be argued that species LXV is on the path of the reverse Diels-Alder reaction, but that similar opportunities are available only to Diels-Alder dimers because of the special structural features which relate them to the Cope rearrangement (cf., p. 54). This point of view leads to the idea of a continuum of mechanisms for the Diels-Alder reaction (74b,101), represented at one extreme by the symmetrical one-step mechanism and at the opposite by a mechanism such as that proposed by Woodward and Katz. These authors in fact admit the possibility that some Diels-Alder additions may involve a second energy barrier in the formation of the second bond (cf. step (4)), whereas others do not.

The firmest conclusion which the experiments with optically active labeled methacrolein dimer permit is the unequivocal exclusion of an open-chain diradical intermediate, such as LXVI, as being important in the Diels-Alder reaction of methacrolein or dissociation of



LXVI

the dimer. Species LXVI is symmetric and would lead to racemization of the undissociated dimer, whereas essentially complete retention of optical activity is observed. This conclusion makes it highly improbable that open-chain diradicals (or linear intermediates of any kind) are involved in other Diels-Alder reactions.

Summary.— There is at present no all-embracing mechanistic picture which readily accounts for the available evidence concerning the mechanism of the Diels-Alder reaction. The evidence strongly favors an unsymmetrical bond-forming process, with one of the new bonds largely or completely formed while the other is in the process of formation. A linear diradical intermediate has been rigorously ruled out as taking part in the Diels-Alder reaction of methacrolein, and is probably not involved in other Diels-Alder reactions.

Experimental

Methacrolein Dimer (2,5-Dimethyl-3,4-dihydro-1,2-pyran-2-aldehyde).— The procedure was based on that of Stoner and McNulty (105) (cf. that of Whetstone (106)). Freshly distilled methacrolein (144 g., 2.05 moles) containing 1% of hydroquinone was heated under autogenous pressure at 130-140° for 8 hr. in a 500-ml. stainless-steel autoclave. Distillation through a short Vigreux column yielded 43 g. of recovered methacrolein and 83 g. (82% yield, 58% conversion) of methacrolein dimer, b.p. 64-66° (19 mm.), n_D^{25} 1.4514 (lit. (105) b.p. 63° (20 mm.), n_D^{20} 1.454). Analysis by v.p.c. (Column K, 143°) indicated a product of about 99% purity. The carbonyl absorption in the infrared spectrum occurred at 1735 cm.⁻¹ and double-bond absorption at 1668 cm.⁻¹.

Cannizzaro Reaction of Methacrolein Dimer.— The procedure was based on those given in references 105 and 106. Methacrolein dimer (170 g., 1.21 mole) was added dropwise to 115 g. (2.87 mole) of sodium hydroxide as a 40% aqueous solution. The mixture was stirred by hand during the addition (it became progressively more viscous), and was maintained at 40-50° by cooling in ice (the temperature rose to 70° at one point). The semi-solid mass was stirred with 170 ml. of water to dissolve the solids, and the resultant mixture was extracted with four

250-ml. portions of ether. The combined extracts were discarded.

The aqueous layer was cooled in an ice-salt bath and maintained at 5-10° during neutralization (to about pH 2) by the dropwise addition of 30% sulfuric acid. The resultant sludge was extracted with four 250-ml. portions of ether, and the combined ether solutions were concentrated in a stream of air, then under reduced pressure using a rotary evaporator. Two 15-ml. portions of pentane were added to the viscous residue and each was pumped off again. Crystallization was induced by removal of the last of the solvent under high vacuum. The crude acid was recrystallized from petroleum ether and yielded, in three crops, 76.3 g. of 2,5-dimethyl-3,4-dihydro-1,2-pyran-2-carboxylic acid, in 90% of the theoretical yield. A sample of the acid recrystallized further from petroleum ether had m.p. 62.5-64° (lit. (106) m.p. 61-62.5°). Infrared carbonyl absorption occurred at 1718 cm^{-1} , double-bond at 1674 cm^{-1} ; a weak band at 1780 cm^{-1} was unassigned.

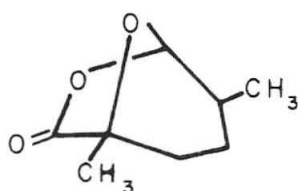
Resolution of 2,5-Dimethyl-3,4-dihydro-1,2-pyran-2-carboxylic Acid.— A solution of the brucine salt was prepared by adding 110 g. (0.704 mole) of the acid to a slurry of 278 g. (0.706 mole) of brucine in 550 ml. of reagent-grade acetone, and heating at reflux for a few minutes to dissolve the solids completely. The solution was refrigerated, and crystallization allowed to take place over the period of several days. The supernatant liquid was decanted from the hard solid cake which was then recrystallized from methanol; 155 g. of the brucine salt was obtained

in four crops.

The separate crops were combined, and 128 g. (0.232 mole) of the mixture dissolved in 800 ml. of warm water. The solution was cooled in an ice bath and maintained at 0-10° during neutralization (to about pH 2) by the dropwise addition of 10% hydrochloric acid. Extraction of the acid solution with 1000 ml. of ether in five portions, and evaporation of the combined ether extracts in a stream of air followed by pumping under high vacuum afforded 33.7 g. (93%) of the acid as a viscous liquid which could not be induced to crystallize. Its infrared spectrum was virtually identical to that of a sample of the solid d,l-acid, and its optical rotation was found to be $[\alpha]^{25}_D - 23.0^\circ$ ($c = 4.35$ in 95% ethanol).

2,5-Dimethyl-3,4-dihydro-1,2-pyran-2-carbonyl Chloride.-

In several preliminary attempts to prepare the acid chloride by reaction of the acid with thionyl chloride, it was found that the first-formed hydrochloric acid by-product catalyzed the conversion of the remaining acid to a lactone (infrared carbonyl absorption at 1805 cm.^{-1}) which had the probable structure (105,107) shown below. The lactone was pre-



pared independently by treating an ether solution of the acid with a catalytic amount of hydrochloric acid.

The acid chloride was prepared successfully by a modification of the procedure given by Wilds and Shunk (108). The sodium salt was prepared by neutralizing 33.7 g. (0.216 mole) of the optically active acid dissolved in 50% aqueous methanol, removing the solvent under reduced pressure (rotary evaporator) and drying overnight at 65° (< 1 mm.) over phosphorous pentoxide. The dry powdered salt was suspended with magnetic stirring in 400 ml. of anhydrous ether containing 1.5 ml. of pyridine, and the mixture chilled in an ice-salt bath. When a thermometer immersed in the suspension registered -10°, 34 ml. (about 47 g., 0.37 mole) of freshly distilled oxalyl chloride (60.5°) was added dropwise as rapidly as the immediate evolution of gas permitted. The reaction mixture, which had warmed up to 5° during the addition, was stirred for a few minutes and allowed to warm up to 20°. The ether and excess oxalyl chloride were removed under the reduced pressure of a water aspirator, then a few ml. of benzene was added and removed with an oil pump. The residue was taken up in 80 ml. of benzene and filtered; the filtrate was pumped at reduced pressure to remove several ml. of the solvent, and was used directly in the following preparation. In a preliminary experiment, the acid chloride was isolated and found to exhibit infrared carbonyl absorption at 1780 cm.^{-1} and double-bond absorption at 1675 cm.^{-1} ; a band at 1825 cm.^{-1} was unassigned.

2,5-Dimethyl-3,4-dihydro-1,2-pyran-2-(N-methyl-N-phenyl)-
amide.— The benzene solution from the above preparation was chilled in an ice bath and swirled by hand during the dropwise addition of a solution of 23.2 g. (0.217 mole) of N-methylaniline and 17.1 g. (0.216 mole) of pyridine in 20 ml. of benzene. The resulting viscous mixture was heated to 60° and maintained at that temperature for 10 min., then cooled to room temperature and poured into 50 ml. of 5% hydrochloric acid. The organic layer was separated and washed successively with saturated sodium bicarbonate solution and water. It was found by infrared spectroscopy that there still remained a considerable amount of unreacted acid chloride, so a one-to-one (molar) mixture of N-methylaniline and pyridine was added to the wet benzene solution until the odor of pyridine could be detected above it. About 7 g. (0.06 mole) of N-methylaniline was added. (Apparently the acid chloride contained some residual oxalyl chloride which consumed part of the N-methylaniline. This difficulty was not encountered in several pilot reactions.)

The wet benzene solution was washed consecutively with acid, base and water, then distilled directly to remove most of the solvent. The residue was distilled at 1.5 mm. through a short head without a condenser and yielded, in addition to 3.2 g. of forerun, 36.9 g. (70% yield from the acid) of semisolid which was recrystallized from n-hexane and afforded 30.9 g. of product in four crops.

A sample of the d,l material recrystallized twice from n-hexane had m.p. 58-59.6°.

Anal. Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71.

Found: C, 73.74; H, 7.83; N, 6.08.

2,5-Dimethyl-3,4-dihydro-1,2-pyran-2-(2H -aldehyde).— The procedure was based on that of Weygand et al. (109). A magnetically stirred solution of 30.0 g. (0.122 mole) of the optically active amide in 300 ml. of anhydrous ether was chilled in an ice-bath and maintained at -15 to -10° during the addition over 1.5 hr. from a powder-addition funnel of 3.0 g. (0.072 mole) of lithium aluminum deuteride. The mixture was stirred at 0° for five hours after the completion of addition, then cooled to -10° and the excess lithium aluminum deuteride decomposed with water.

Following acidification of the mixture with 10% sulfuric acid, the ether layer was separated and the aqueous layer extracted with three 80-ml. portions of ether which were combined with the principal ether solution, washed with 40 ml. of 5% sulfuric acid, filtered through a bed of anhydrous sodium sulfate and dried over anhydrous sodium sulfate. The ether was removed by distillation, and the residue was flash distilled at 1 mm. and collected at -78°. It was redistilled using a 30-cm. wire-spiral-packed column and yielded 10.8 g. (63% yield) of material in five fractions boiling at 52-56° (11-13 mm.). The infrared spectra of the fractions were virtually identical, as were the indices of refraction

(\underline{n}^{25}_D 1.4511-1.4514), and v.p.c. analysis (Column K, 145°) showed that each contained about the same amount of impurity (less than 1%) which appeared as a broad flat peak just before the main peak. The infrared carbonyl absorption occurred at 1720 cm^{-1} and the double bond absorption at 1667 cm^{-1} . The n.m.r spectra exhibited no resonance absorption in the region expected for the aldehyde proton.

The samples were stored at 5° in an atmosphere of nitrogen, and the separate portions used in the rearrangement reactions were flash distilled immediately before use.

Rearrangement of Methacrolein Dimer at Atmospheric Pressure.

A 1.5-g. sample of optically active deuterium-labeled methacrolein dimer was flash distilled at 12 mm. and the optical activity measured; $\underline{\alpha}^{27}_D - 71.35 \pm 0.05^\circ$ (neat, $l = 1$ dm). A portion (1.329 g.) was carefully weighed into a 10-ml. flask, 10.0 mg. of hydroquinone added (0.75%), and the mixture heated at reflux (171°) for 9 hr., with the thermometer bulb immersed in the boiling liquid. The methacrolein which formed passed through a steam-heated reflux condenser and was condensed at -78°; 41 mg. was collected. It was identified by a comparison of its infrared and n.m.r. spectra and v.p.c. retention time with those of an authentic sample. The weight of dimer remaining at the end of 9 hr. was 1.154 g., leaving 134 mg. to be accounted for by sample adhering (visibly) to the walls of the apparatus.

The rearranged dimer was found by n.m.r. to contain residual methacrolein, and was twice distilled at 12 mm. through a short micro

column. Each time, a few drops of forerun was removed before the main fraction was collected. Its optical activity was found to be $\alpha_{\text{D}}^{30} -70.59 \pm 0.06^\circ$ (neat, $l = 1$ dm) after the first distillation and $\alpha_{\text{D}}^{26} -71.00 \pm 0.04^\circ$ (neat, $l = 1$ dm) after the second. The latter value represents a 99.5% retention of optical activity.

The weight of the distillation residue, after it was dried overnight at 60° (1 mm.) was 54 mg. (not including hydroquinone), or 4.1% of the total dimer taken.

It was found by electronic integration of the aldehyde and vinyl proton n.m.r. resonances (cf. Fig. 2-A) that $28.8 \pm 0.5\%$ (standard deviation in twenty-four consecutive determinations) of the rearranged dimer contained a proton in the aldehyde function.

Rearrangement of Methacrolein Dimer in a Sealed Tube.— A sample of flash-distilled optically active deuterium-labeled methacrolein dimer (1.1973 g.) having $\alpha_{\text{D}}^{26} -71.44 \pm 0.05^\circ$ (neat, $l = 1$ dm) was sealed into an n.m.r. tube with 10.5 mg. (0.87%) of hydroquinone and heated at $180 \pm 1^\circ$ for 7 hr. The n.m.r. spectrum of the rearranged sample is given in Figure 2-B. The areas of the aldehyde and vinyl proton absorption resonances of the dimer and of methacrolein were integrated electronically in twenty-four consecutive determinations and gave the following relative values (expressed in mm.; the standard deviation is given): 53.0 ± 1.1 for the sum of the aldehyde proton resonances of the dimer and methacrolein, 83.9 ± 0.8 for the vinyl proton resonance

of the dimer plus one vinyl proton resonance of methacrolein buried under that of the dimer, and 17.5 ± 0.8 for the remaining vinyl proton resonance of methacrolein. The sum of the aldehyde and vinyl proton resonances of the dimer plus one vinyl proton resonance of methacrolein was 128.1 ± 2.3 , giving the value 13.7 ± 0.9 for the mole percent of methacrolein in the mixture.

The reaction product mixture was twice distilled at 14 mm., each time removing a few drops of forerun (it was found by n. m. r. that one distillation did not remove the methacrolein effectively), and the optical activity of the distillate found to be $\alpha_D^{31} - 60.83 \pm 0.05^\circ$ (neat, $l = 1$ dm). The distillation residue, after drying at 60° (1 mm.), weighed 31.9 mg., (not including hydroquinone, but including traces of silicone grease from the distillation), or 2.7% of the weight of dimer taken. In a preliminary rearrangement carried out in the absence of polymerization inhibitor, 30% of the dimer taken was converted to polymer in 7 hr. at 180° .

The n. m. r. spectrum of the distillate was examined and the extent of rearrangement determined by electronic integration of the aldehyde and vinyl proton resonances. It was found that $39.8 \pm 0.4\%$ (standard deviation in twenty-four consecutive determinations) of the dimer contained the proton in the aldehyde functional group.

The distillate was examined mass spectrometrically to determine

the amounts of non-deuterated and di-deuterated material formed in the reaction. The spectrum of the rearranged material was compared with that of the unrearranged dimer, taking into account only the relative heights of those peaks with mass numbers of approximately 140, 141 and 142 for the unfragmented non-deuterated, mono-deuterated, and di-deuterated molecules, respectively. Minor changes in the peaks representing the approximate mass numbers, 138, 139, 143 and 144, were not considered. For the unrearranged dimer, the relevant peaks had the following heights: 140, 9.9 mm.; 141, 790 mm.; 142, 71.3 mm. The following was observed for the rearranged material: 140, 40.6 mm.; 141, 788 mm.; 142, 102.5 mm. These values indicate 3.30% of non-deuterated and 3.35% of di-deuterated molecules in the distilled rearranged dimer mixture, or 2.85 and 2.89 mole percent, respectively, in the total rearrangement product mixture.

The samples of unrearranged and rearranged dimers described above were re-analyzed mass spectrometrically about two weeks after the original analysis, during which time they remained at room temperature unprotected from the atmosphere. Changes were observed in the spectra of both samples, and the average amounts of non-deuterated and di-deuterated molecules in the distilled rearranged material, as calculated above, were found to be 3.35% and 4.60%, respectively. The reason for the change in the spectra was not established (110).

Appendix I

Melting points are uncorrected and were taken either in capillary tubes in an electrically heated stirred oil bath or, where indicated, using a Reichert Kofler Block apparatus. Boiling points are uncorrected. Infrared absorption spectra were determined using a Beckman Model IR-7 Spectrophotometer, and nuclear magnetic resonance spectra were obtained at 60 Mc with a Varian Associates V-4300B high resolution spectrometer with a 12-in. magnet and equipped with a flux stabilizer, field homogeneity coils and electronic integrator. Vapor phase chromatography was carried out with a Perkin-Elmer Vapor Fractometer, Model 154-C. The column designations refer to the following stationary phases: Column A, diisodecyl phthalate; Column C, dimethylsiloxane polymer (silicone oil DC-200); Column K, polyethylene glycol (Carbowax 1500).

Appendix II

Approximate Rate Constants for Non-dissociative Rearrangement(k_r) and Dissociation (k_d) of Methacrolein Dimer at 180° (cf. p. 62)Rearrangement

Optically active XIII = $48.5 - 2.9 = 45.6\%$ of total product.

Optically active XV = $32.1 - 2.9 = \frac{29.2\%}{74.8\%}$ of total product.

Fraction of XIII = 0.610.

Fraction of XV = 0.390.

Integrated rate equation for opposing first-order reactions:

$$\ln \frac{A-B}{A_0} = -2 k_r t.$$

Assuming $A_0 = 1.000$ = concentration of XIII at $t = 0$,

then $A = 0.610$ = concentration of XIII at $t = 420$ min.

and $B = 0.390$ = concentration of XV at $t = 420$ min.

$$k_r = 1.8 \times 10^{-3} \text{ min.}^{-1}$$

Dissociation

Dissociation yields only optically inactive materials. In 100 moles of reaction product, there are 13.7 moles of methacrolein (representing 6.9 moles of dimer) and $2.87 \times 4 = 11.5$ moles

of optically inactive dimer; 100 moles of product represents
 $100 - 6.9 = 93.1$ moles of starting dimer.

Fraction of starting dimer dissociated = $(6.9 + 11.5)/93.1 =$
 0.198 .

Integrated rate equation for first-order reaction: $\ln \frac{A}{A_0} = -k_d t$.

Assuming $A_0 = 1.000$ = concentration of starting dimer at
 $t = 0$, then $A = 0.802$ = concentration of undissociated
dimer at $t = 420$ min.

$$k_d = 5.2 \times 10^{-4} \text{ min.}^{-1}$$

$$\frac{k_r}{k_d} = e^{\frac{\Delta F_d - \Delta F_r}{RT}}$$

where ΔF_d and ΔF_r are the free energies of activation,
respectively, of dissociation and rearrangement, R = gas
constant (1.99 cal./deg. mole) and T = absolute temperature.

$$\Delta F_d - \Delta F_r = 1.1 \text{ kcal. per mole.}$$

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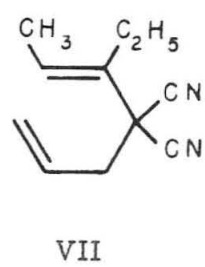
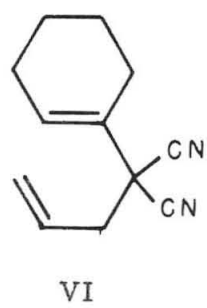
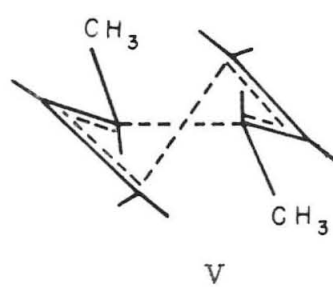
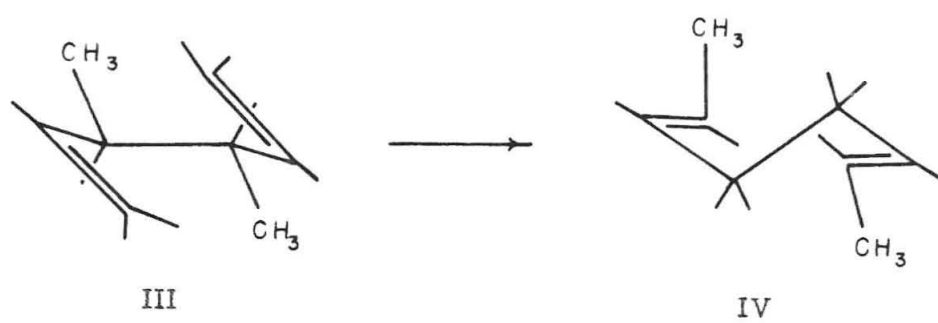
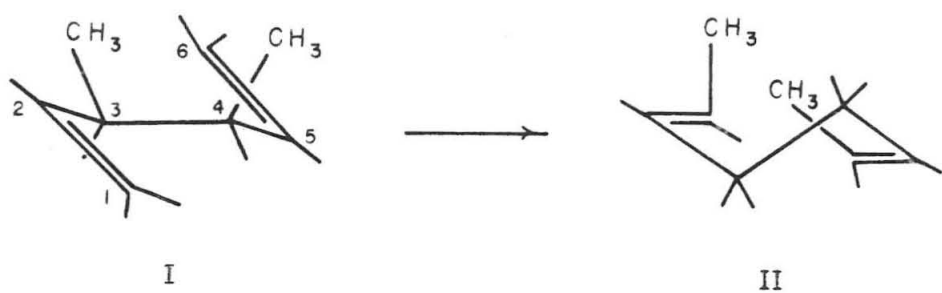
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PROPOSITIONS

1. There seems no longer to be much doubt that the Cope rearrangement (1), illustrated by the thermal conversion of 3,4-dimethyl-1,5-hexadiene (cf. I and III) to 1,6-dimethyl-1,5-hexadiene, is an intramolecular rearrangement involving a transition state of rigid geometry. Convincing evidence is the observation that meso-3,4-dimethyl-1,5-hexadiene (I) rearranges virtually exclusively to cis-trans-1,6-dimethyl-1,5-hexadiene (II) whereas the racemic 3,4-dimethyl derivative (III) forms the trans-trans isomer (IV) (2). The stereochemistry seems compatible only with a transition state having a configuration resembling V (for the rearrangement of III).

Still an open question, however, is the degree of bond breaking and bond formation in the transition state. It is usually assumed (1,3) that these processes are concerted, i.e., that rehybridization from \underline{sp}^2 to \underline{sp}^3 at C-1 and C-6 occurs simultaneously with a change from \underline{sp}^3 to \underline{sp}^2 at C-3 and C-4. The evidence is by no means compelling. The experimental observations, including that discussed above, may be accommodated by assuming a restricted configuration resembling V in a radical-pair intermediate, where the hybridization at C-1 and C-6 is still largely \underline{sp}^2 whereas that at C-3 and C-4 has been converted from \underline{sp}^3 to \underline{sp}^2 . A potential means of deciding between the two pictures is provided by secondary hydrogen isotope effects (4).



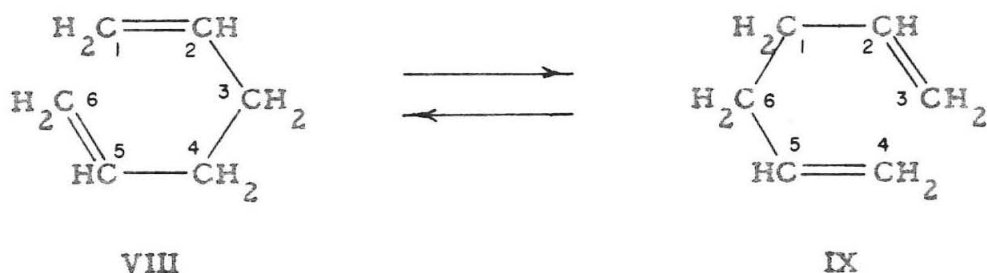
A current theory (5) predicts that the reaction rate of a compound possessing a C-H bond which is not broken in the rate-determining step but which undergoes a hybridization change from sp^3 in the ground state to sp^2 in the transition state, will decrease (normal isotope effect) if the hydrogen is substituted by deuterium. Conversely, if the change is from sp^2 to sp^3 , deuterium substitution should cause an increase in rate (inverse isotope effect). In the Cope rearrangement, substitution of deuterium at C-1 and C-6 should result in an inverse isotope effect if the reaction process is concerted, but no isotope effect if a species such as a radical pair is involved. A normal isotope effect due to deuterium at C-3 and C-4 is expected on the basis of either mechanistic picture.

Systems suitable for study would be appropriately substituted 1-cyclohexenyl allylmalonitrile (VI) or 1-ethylpropenyl allylmalonitrile (VII), both of which rearrange by first-order processes having substantial rates at 120° (1). To enhance the magnitude of any potential isotope effects, the isomerizations could undoubtedly be examined at temperatures below 100°. The isotope effects should be separately measured with samples deuterated in the positions corresponding both to C-1 or C-6, and C-3 or C-4.

The stereospecific rearrangements of the meso and racemic 3,4-dimethyl-1,5-hexadienes suggest that the reversibility of the Cope rearrangement might be examined by attempting to convert the cis-trans

and trans-trans products to the corresponding starting isomers. The reactions $\text{II} \rightarrow \text{I}$ and $\text{IV} \rightarrow \text{III}$ should take place at higher temperatures than the reverse processes. Reversibility has been demonstrated in the interconversions of 3-methyl-1,5-hexadiene and 1-methyl-1,5-hexadiene (6), and an obvious extension would be to determine the stereospecificity of the reverse reactions.

2. At about 300° (7), 1,5-hexadiene (VIII) should undergo a reversible Cope rearrangement (1) to IX, a transformation which could



not be detected chemically unless the starting material were isotopically substituted. At higher temperatures, the reaction would take place at an increasingly rapid rate until the 1,5-hexadiene began to dissociate into allyl radicals; this dissociation begins at $690-700^\circ$ and is complete at 890° (8). At temperatures above 300° but below 690° , the system presents a unique opportunity for detecting spectrophotometrically the high-energy species involved in the interconversion.

The probable configuration of this high-energy species, X (the unsubstituted analog of V) is discussed in the previous proposition.

It is expected to exhibit ultraviolet absorption at about 2200 Å, close to the value for butadiene, whereas the parent 1,5-hexadiene has its principal absorption near 1750 Å (9).

An estimate of the concentration of X at 500° may be made from transition-state theory (10), using the equation $k_r = \frac{kT}{h} K^*$, where k_r is the first-order rate constant for rearrangement, k the Boltzmann constant, T the absolute temperature, h equals Planck's constant, and K^* a constant having the form of an equilibrium constant and relating the concentration of the transition state to that of unexcited 1,5-hexadiene. The rate constant, k_r , may be estimated from the familiar Arrhenius equation, $k_r = A e^{-\frac{\Delta E}{RT}}$, where ΔE represents an activation energy, R equals the gas constant, T the absolute temperature and A a frequency factor having the same units as k_r . If it is assumed that $\Delta E = 35$ kcal. per mole (the highest known value is 28.6 kcal. per mole for the rearrangement of ethyl(1,3-dimethyl-1-butenyl)allylcynoacetate) and $A = 10^{11}$ sec.⁻¹ (close to the values observed for three different Cope rearrangements) (1), k_r at 500° is approximately 10 sec.⁻¹. The value for K^* at this temperature is then about 6×10^{-13} . The concentration of 1,5-hexadiene in the pure liquid at 500° is about 6M, so that the concentration of transition state would be 4×10^{-12} M.

To detect ultraviolet absorption from a species of this low concentration, an extremely long path length would be required, possibly best obtained using a multi-pass cell (11, 12). Assuming as the lower

practicable limit for optical density (D) the value 5×10^{-3} , a path length (l) of 2×10^4 cm. and a molar absorption coefficient (ϵ) for the transition state of 10^5 (probably a slightly high estimate), the detectable concentration (c) calculated from the Beer-Lambert absorption law, $D = \epsilon cl$, is 3×10^{-12} M. This corresponds sufficiently well with the estimated concentration of transition state, 4×10^{-12} M, to suggest that it might actually be detected.

The experiment proposed is admittedly fraught with practical difficulties and a certain amount of improbability. The hot bands of the parent 1,5-hexadiene might interfere at that temperature, but a careful examination of intensity versus temperature in the region about 2200 \AA should reveal absorption by the transition state even if it is superimposed on the spectrum of 1,5-hexadiene.

1,5-Hexadiene may prove to be an unfavorable case for detection of the transition state. Larger rate constants and consequently larger concentrations could be obtained with appropriately substituted 1,5-hexadienes, but the substituents which enhance the rate of rearrangement would be expected to lower the temperature at which dissociation into allyl radicals occurred.

3. Swain and co-workers (13) have proposed that the effect of substituents on the magnitude of primary hydrogen isotope effects (14) may be used to distinguish between proton-transfer and hydride-transfer

transition states. In brief, the argument states that the bonds in the transition state, $R-H-R'$, for proton transfer should be longer, weaker, more ionic and more polarizable than those in the corresponding transition state for hydride transfer, and hence should be more strongly affected by substituents on R and R' . Substituent effects on the bonding in $R-H-R'$ would be reflected by changes in the magnitude of k_H/k_D (where the k 's refer to reaction rate constants for the undeuterated and appropriately deuterated compounds). For a proton transfer, k_H/k_D is expected to vary as the electronic character of the substituents is changed. In a hydride transfer, expected to have strong, short, highly covalent and non-polarizable bonds in the transition state, the substituents on R and R' should have little effect on the bonding and a negligible effect on the value of k_H/k_D .

Substituent effects on k_H/k_D for the oxidation of 2-propanol to acetone with bromine in water at 50° were examined (13a) and the following rate constant ratios observed:

$$\frac{k_{2\text{-propanol}}}{k_{2\text{-propanol-2-d-ol}}} = 2.94$$

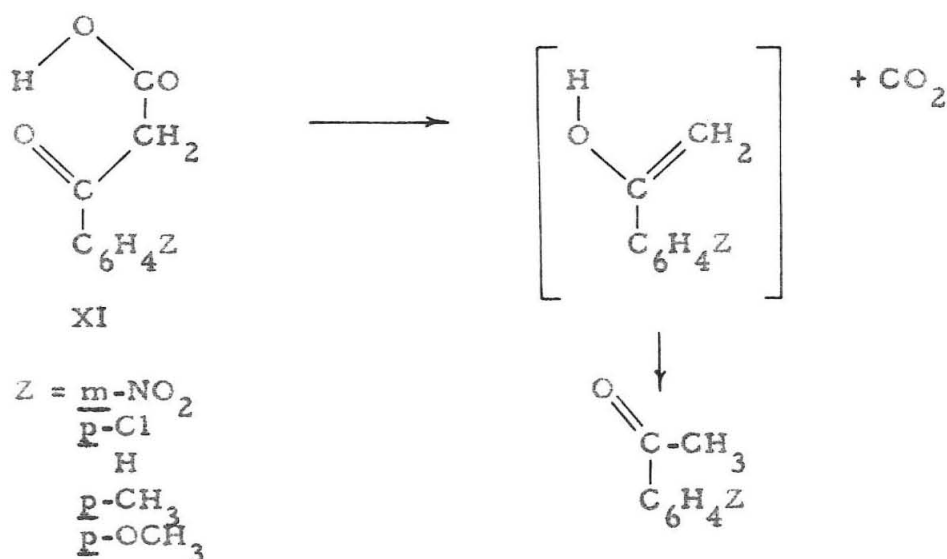
$$\frac{k_{2\text{-propanol}}}{k_{2\text{-propanol-d}}} = 1.49$$

$$\frac{k_{1\text{-fluoro-2-propanol}}}{k_{1\text{-fluoro-2-propan-2-d-ol}}} = 2.83$$

$$\frac{k_{1\text{-fluoro-2-propanol}}}{k_{1\text{-fluoro-2-propanol-d}}} = 2.06$$

Since the effect of fluorine on the CH isotope effect was within experimental error, it was concluded, on the basis of the argument cited, that this hydrogen is transferred as a hydride. The considerable change in the OH isotope effect with the introduction of fluorine was taken as evidence that the alcoholic hydrogen is transferred as a proton.

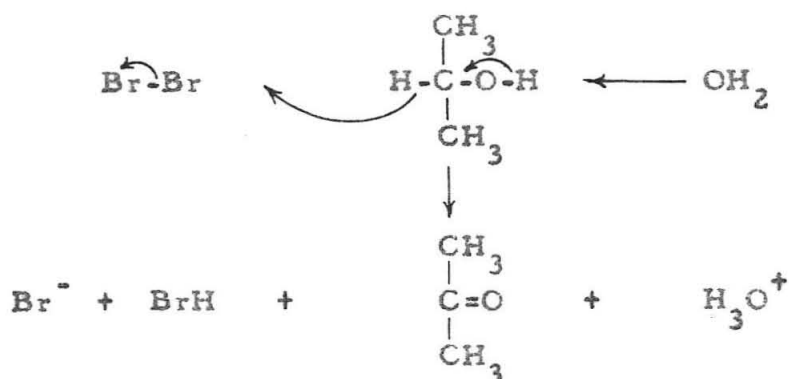
Also examined was the effect of substituents on k_H/k_D for the decarboxylation of substituted benzoylacetic acids (XI), assumed to proceed through a cyclic mechanism (13b). The OH isotope effect varied from 2.8 for the m-nitro compound to 0.85 for the p-methyl, and led to the conclusion that the electron distribution in the OHO group at the transition state corresponded to that expected for a proton transfer.



The use of substituent effects on primary isotope effects to distinguish between proton and hydride transfers is potentially a valuable tool in establishing this particular aspect of reaction mechanisms.

However, before it may be accepted as generally valid, other reaction systems must be studied and the mechanistic conclusions tested by other means if possible. In both of the systems examined by Swain et al., secondary deuterium isotope effects should provide useful information, either supporting or militating against the conclusions reached.

From the data on primary isotope effects, the mechanism for oxidation of 2-propanol was described as follows:



The low value for the OH isotope effect (1.49) suggested that transfer of the alcoholic proton had not begun or had only barely begun in the transition state, whereas the much larger CH isotope effect (2.94) showed that this bond was broken in the transition state. The net result would be accumulation of positive charge at the central carbon atom.

Formation of a positive charge at C-2 might be verified by an examination of secondary isotope effects (4), comparing the rates of oxidation of 2-propanol and 1- d_3 -2-propanol. The rate of the former should be the greater. (Rate retardation due to deuterium substitution at a position adjacent to a center which bears a positive charge in the

transition state is the well known β -deuterium isotope effect, generally attributed to the influence of hyperconjugation on CH vibration frequencies (15)). A similar rate comparison between 1-fluoro-2-propanol and 1-fluoro-3- d_3 -2-propanol should show a smaller β -isotope effect, since the value of the primary OH effect (2.09) indicates that transfer of the proton in the transition state has taken place to a greater degree than with the unfluorinated alcohol, and consequently that there is less positive charge at C-2.

According to the cyclic mechanism assumed for the decarboxylation of the benzoylacetic acids, the sp^3 hybridization at the methylene carbon is partially converted to sp^2 in the transition state. Deuterium substitution at a center undergoing this transformation is expected to decrease the reaction rate (cf. Proposition 1), but Swain et al. reported (13b) that the rates of decarboxylation of benzoylacetic acid- d and benzoylacetic- d_2 acid- d were identical within experimental error. (The trideuterated derivative was examined only to determine what kinetic complications might result from the possible incorporation of deuterium in the methylene groups during synthesis of the acids.) The absence of a secondary isotope effect suggests that the cyclic mechanism may not be the correct one (16). The trideuterated derivatives of the other substituted acids should be prepared, and the isotope effects compared with those of the acids monodeuterated in the carboxyl group. If the absence of a secondary effect proves to be general, the concerted cyclic

mechanism would be suspect and the presumed distinction between hydride- and proton-transfer transition states no longer valid.

4. Photosensitization of bicycloheptadiene (XII) with acetophenone in the triplet state (17) leads to XIII (18). It is proposed that the unknown cubane (XIV) and its derivatives may be prepared by an analogous reaction.

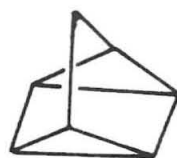
A probable immediate precursor to octamethylcubane is the known compound, syn-octamethyltricyclooctadiene (XV) (19). By analogy with XII, the diradical formed in the photosensitization should close to yield a four-membered ring, resulting in the desired octamethylcubane.

Unsubstituted cubane might be prepared directly by the photosensitization of cyclooctatetraene, XVI, conformationally suited (20) to form the analog of XV, followed by final closure to cubane.

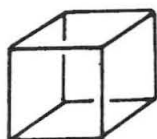
5. On the basis of the available evidence concerning the mechanism of the Diels-Alder reaction (21), the addition of trans-1-phenylbutadiene and a dienophile such as acrylyl chloride should proceed through species XVIIa (whose precise position on the energy profile is undefined; dotted lines represent either partial bonds or the so-called secondary attractive forces (22)) to yield the "ortho" cis-adduct, XVIIIa. When the reaction is carried out at room temperature, XVIIIa is indeed



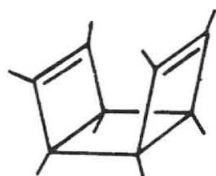
XII



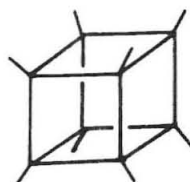
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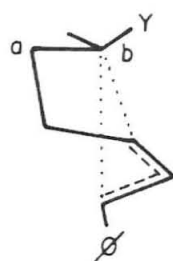
XIV



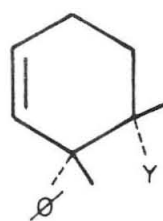
XV



XVI

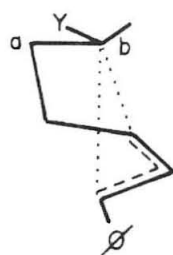


XVII

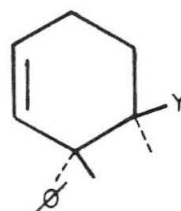


XVIII

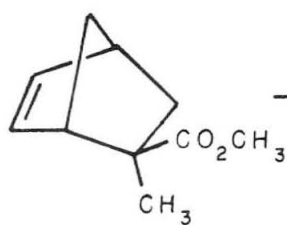
a) $Y = \text{COCl}$
b) $Y = \text{CO}_2\text{CH}_3$



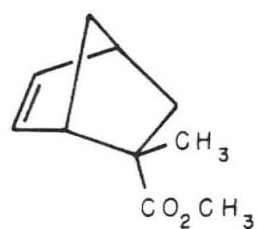
XIX



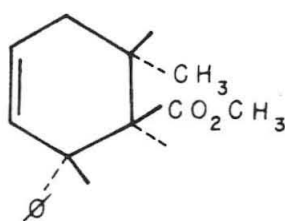
XX



XXI



XXII



XXIII

the observed product (23), but at temperatures over 100°, the trans-adduct (XXb) is also formed (23), presumably through species XIXb. The cis-adduct may also be converted to the trans by distillation at 170° (25 mm.) (23), conditions under which any acrylyl chloride (b.p. 75° (1 atm.)), if it formed, would have distilled out of solution before reacting significantly to yield the trans isomer.

trans-1-Phenylbutadiene also yields mixtures of analogous cis and trans isomers with methyl acrylate (24), methyl methacrylate (24), acrylic acid (25), acrylamide (23) and methyl vinyl ketone (26), but the interconversion of the cis and trans forms has not been studied.

It is proposed that the cis adducts when prepared optically active may be converted thermally to the trans isomers with preservation of optical activity, by a pathway which represents a partial reverse Diels-Alder reaction, involving formation of analogs of XVII followed by rotation about bond ab to give analogs of XIX which yield the trans isomers. The same type of internal isomerization was not observed in the conversion of the optically active exo adduct (XXI) of methyl methacrylate and cyclopentadiene to the corresponding endo compound (XXII); the product was completely racemic, indicating that the isomerization took place by dissociation to the addends followed by recombination (27). However, this case is not a favorable one, since rotation about bond ab in a species analogous to XVII would be severely hindered by the methyl group.

A convenient example for study would be the optically active cis adduct (XVIIIb) of trans-1-phenylbutadiene and methyl acrylate, which could be prepared by resolution of the cis adduct of acrylic acid followed by esterification. It would be a better system for study than the acrylyl chloride adduct, since the isomerization of the latter could conceivably be due to catalysis by traces of acid, formed by reaction of the chloride with moisture in the system.

Observation of the isomerization as anticipated would be an important contribution toward elucidating the precise nature of the high-energy species involved in the Diels-Alder reaction and would be most readily explained by species such as XVIIIb and XIXb. If the internal isomerization is observed under conditions where there is significant competitive formation of addends by the reverse Diels-Alder reaction (rendered irreversible by immediate distillation of one or both of the reactants out of solution) and the unreacted cis adduct is found to have retained its original activity, it would provide confirming evidence for the exclusion of a linear intermediate (which is symmetric and would lead to racemization of the undissociated adduct) as being involved in the Diels-Alder reaction. This has been shown to be the case in the Diels-Alder dimerization of methacrolein (28), but the additional evidence with an undisputably "typical" Diels-Alder adduct is necessary as the death blow to linear intermediates in the Diels-Alder reaction.

If the internal isomerization is observed as what appears to be a partial reverse Diels-Alder reaction, it would represent a violation, as yet undetected, of the rule of cis addition (which states that the stereochemical relationships of substituents at a and b (cf. XVII) in the dienophile are preserved in the product). In this case, a careful examination of the Diels-Alder additions of trans-1-phenylbutadiene and dienophiles such as methyl cis- β -methylacrylate should be undertaken in an attempt to detect kinetically controlled products such as XXIII, in which the original cis relationship of the methyl and carbomethoxy groups is not maintained.

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